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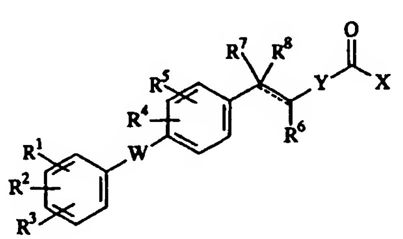
(54) Title: PHARMACEUTICAL AGENTS



(I)

(57) Abstract: Use of compounds of formula (I) in the manufacture of a medicament for use in treating a disorder mediated by histone deacetylase: wherein the symbol ---- represents a single bond or a double bond or the symbol ---- R^6 and R^8 together represent cyclopropyl and R^1 to R^8 W, X and Y are as defined herein; and pharmaceutically acceptable salts thereof. Also disclosed are compounds for such uses. The compounds are useful in the treatment of cancers. They may be utilised in combination therapies with DNA methylation inhibitors and other anti cancer agents.

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PHARMACEUTICAL AGENTS

The present invention inhibitors of histone deacetylase and the use of such compounds in medicine.

Inhibitors of the enzyme histone deacetylase (HDAC) are a new and promising class of therapeutic agents. HDAC inhibitors are especially promising for cancer therapy since they are able to regulate transcription and induce apoptosis or differentiation in cancer cells and are effective in animal xenograft models. Histones in the nucleus of the cell are complex proteins integrally associated with DNA. Histone deacetylase is acknowledged to be a critical regulator of chromatin structure and gene regulation, and HDAC inhibitors induce hyperacetylation in chromatin that leads to activation of specific genes. Conversely, deacetylation of histones results in repression of transcription. There is increasing evidence that cell proteins involved in the regulation of proliferation and differentiation act by recruiting histone deacetylases (HDAC) and also histone acetyltransferases. Malignancies can arise by aberrant histone acetylation. Fundamental nuclear processes including DNA replication, transcription and repair are influenced by chromatin structure and the binding of regulatory proteins to DNA. These processes can be modulated by altering the extent of acetylation of the ω-amino groups of highly conserved lysine residues in the *N*-terminal tails that protrude from the histone octamer in the nucleus, thereby changing nucleosome conformation and regulating gene expression. Accordingly, HDAC inhibitors could be used in therapy to relieve gene repression and to reinstate the program of cell differentiation and apoptosis, a form of "transcription therapy".

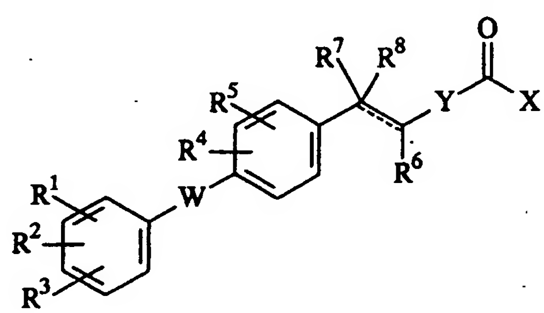
There is intense interest in finding new inhibitors of histone deacetylase (HDAC), especially because most of the early compounds showed severe limitations. Thus, the natural product trichostatin A is thought to mimic such acetylated lysine residues, and its potent inhibition of HDAC is consistent with the binding of its hydroxamic acid unit to a zinc atom in the catalytic pocket of the enzyme. However the high HDAC inhibitory activity of trichostatin A is offset by rapid metabolism to many products, resulting in a short clinical half-life that makes it ineffective for therapy. Sodium phenylbutyrate, a feeble inhibitor of histone deacetylase, was used (together with retinoic acid) to induce complete remission of multi-resistant acute promyelocytic leukaemia (APML) in a patient untreatable by conventional therapy. Depsipeptide is a

potent HDAC inhibitor but exhibited significant cardiotoxicity in clinical trials. Further HDAC inhibitors are disclosed in WO 02/076941.

HDAC inhibitors show promise in countering a variety of cancers including breast and prostate cancer, as well as haematological disorders including leukaemia. HDAC inhibitors are also of potential benefit in the treatment of Huntingdon's disease and possibly other neurological disorders especially Alzheimer's disease, and probably in a wide range of disorders, especially those of genetic and/or metabolic origin. Consequently, potent and metabolically stable HDAC inhibitors of good pharmacological profiles would possess important advantages over current HDAC inhibitors that have usually proved inadequate in clinical trials. WO 02/085400 describes the treatment of diseases associated with aberrant silencing of gene expression, such as cancer, by administration of a HDAC inhibitor and a DNA methylation inhibitor.

A new class of compounds that are HDAC inhibitors has now been prepared in which a saturated, partly saturated or unsaturated alkyl chain is a key feature of the inhibitor and to which is attached a metal-binding terminal group, the other end of the chain typically being linked to an aromatic or heteroaromatic system which is usually of an extended and substituted nature. These HDAC inhibitors can possess superior metabolic stability, lower toxicity or higher potency than previously described and related HDAC inhibitors.

Accordingly, the present invention provides a compound of formula (I):



(I)

wherein:

- the symbol ⎓ represents a single bond or a double bond or the symbol ⎓, R^6 and R^8 together represent cyclopropyl;

- R^1 to R^5 each independently represent hydrogen, C_2-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, C_1-C_{10} hydroxyalkyl, halo, C_1-

C_{10} haloalkyl, amino, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amido, nitro, cyano, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, (C_1-C_{10} alkyl)sulfinyl, (C_1-C_{10} alkyl)sulfonyl or C_1-C_{10} alkyl substituted by amino, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino or di(C_1-C_{10} alkyl)amino;

- R^6 represents hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, an unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double or triple bond, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, halo, cyano, nitro, amino, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amido, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, (C_1-C_{10} alkyl)sulfinyl, (C_1-C_{10} alkyl)sulfonyl, a saturated or unsaturated C_3-C_{12} hydrocarbon chain interrupted by O, S, NR, CO, C=NR, N(R)SO_2, SO_2N(R), N(R)C(O)O, OC(O)N(R), N(R)C(O)N(R), OC(O), C(O)O, OSO_2, SO_2O or OC(O)O where:

  (a) R independently represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, hydroxyl or C_1-C_{10} haloalkyl, and

  (b) the saturated or unsaturated hydrocarbon chain is optionally substituted with C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, hydroxyl, C_1-C_{10} hydroxyalkyl, halo, C_1-C_{10} haloalkyl, amino, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl or C_1-C_{10} alkylsulfonyl;

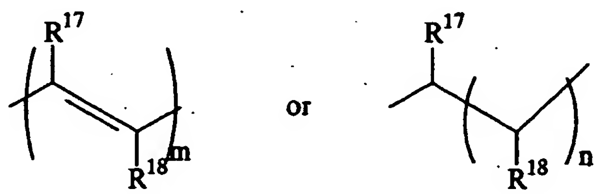
- when the symbol $\overline{}$ represents a single bond, R^7 and R^8 each independently represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} each independently represent hydrogen or C_1-C_6 alkyl or one of R^9 and R^{10} is H and the other is $-CO(C_1$-C_6 alkyl) or R^7 and R^8 together represent =O, $=CH_2$ or $=CHR^9$ wherein R^9 is as defined above;

- when the symbol $\overline{}$ represents a double bond, R^7 represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} are as defined above and R^8 is absent;

- W represents a single bond, $-C(R^{11})=N-$, $-N=C(R^{11})-$, $-C(R^{11})(R^{12})-NR^{13}-$,

$-NR^{13}-C(R^{11})(R^{12})-$, $-CO-NR^{11}-$, $-NR^{11}-CO-$, $-SO_2-NR^{11}-$, $-NR^{11}-SO_2-$, $-C(R^{11})(R^{12})-O-$, $-O-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-S-$, $-S-C(R^{11})(R^{12})-$, -CO-, $-NR^{11}-$, -SO-, $-SO_2-$, O, S or $-[C(R^{11})R^{12}]_p-$ wherein R^{11}, R^{12} and R^{13} each independently represents hydrogen, C_1-C_6 alkyl, C_6 or C_{10} aryl or a 5 to 10-membered heterocylic group and p is an integer of from 1 to 4;

- X represents $-OR^{14}$, $-SR^{14}$, $-NR^{14}OR^{15}$, $-NR^{14}NR^{15}R^{16}$, $-CF_3$, $-CF_2H$ or CH_2F wherein R^{14}, R^{15} and R^{16} each independently represents hydrogen or C_1-C_6 alkyl; and
- Y represents



wherein m is an integer from 1 to 4; n is an integer from 1 to 8; and R^{17} and R^{18} each independently represents hydrogen, unsubstituted or substituted C_1-C_{10} alkyl, an unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double and/or triple bonds, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, halo, cyano, nitro, amino, amido, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, C_1-C_{10} alkylsulfinyl, C_1-C_{10} alkylsulfonyl, or a saturated or unsaturated C_3-C_{12} hydrocarbon chain interrupted by O, S, NR, CO, C(NR), $N(R)SO_2$, $SO_2N(R)$, N(R)C(O)O, OC(O)N(R), N(R)C(O)N(R), OC(O), C(O)O, OSO_2, SO_2O or OC(O)O where R is as defined above and the saturated or unsaturated hydrocarbon chain is optionally substituted as defined above;
and pharmaceutically acceptable salts thereof.

As used herein, a C_1-C_{10} alkyl group or moiety is a linear or branched alkyl group or moiety containing from 1 to 10 carbon atoms, such as a C_1-C_6 alkyl group or moiety or a C_1-C_4 alkyl group or moiety, for example methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

A C_2-C_{10} alkenyl group is typically a C_2-C_6 alkenyl group such as a C_3-C_6 alkenyl group, for example C_3 or C_4 alkenyl and in particular allyl. A C_2-C_{10} alkynyl

group is typically a C_2-C_6 alkynyl group such as a C_3-C_6 alkynyl group, for example C_3 or C_4 alkynyl and in particular propargyl.

A C_1-C_{10} alkoxy group or moiety is a linear or branched alkoxy group or moiety containing from 1 to 10 carbon atoms, such as a C_1-C_6 alkoxy group or moiety or a C_1-C_4 alkoxy group or moiety. The C_1-C_4 alkoxy group may be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy or i-butoxy, preferably methoxy or ethoxy.

As used herein, halo is typically chlorine, fluorine, bromine or iodine and is preferably chlorine or fluorine. A C_1-C_{10} haloalkyl group is typically a said C_1-C_{10} alkyl group, for example a C_1-C_6 alkyl group or C_1-C_4 alkyl group, substituted by one or more said halo atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl groups include perhaloalkyl groups such as $-CX_3$ wherein X is a said halogen atom. Particularly preferred haloalkyl groups are $-CF_3$ and $-CCl_3$.

A substituted C_1-C_{10} alkyl group is typically a said C_1-C_{10} alkyl group, for example a C_1-C_6 alkyl group or a C_1-C_4 alkyl group, substituted by one or more, for example from one to three, atoms or other groups such as hydroxy, halo, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino. The substituted C_1-C_{10} alkyl group may be a said C_1-C_{10} haloalkyl group. Other suitable substituted C_1-C_{10} alkyl groups include C_1-C_{10} hydroxyalkyl.

An unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double or triple bonds is typically a said C_2-C_{10} alkenyl or C_2-C_{10} alkynyl group.

A C_6 or C_{10} aryl group or moiety is typically a phenyl or naphthyl group or moiety. The group or moiety may be substituted by one or more, for example from one to three, atoms or groups such as hydroxy, halo, cyano, amido, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino.

A 5- to 10-membered heterocyclic group may be a heteroaryl group. It may therefore be a 5- to 10-membered aromatic, i.e. fully unsaturated, ring such as a 5- or 6-membered ring, containing at least one heteroatom, for example one, two, three or four heteroatoms, selected from O, S and N. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, imidazolyl, pyrazolidinyl, pyrrolyl, oxadiazolyl, oxazyl, isoxazyl, thiadiazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl and pyrazolyl groups.

Alternatively, the 5- to 10-membered heterocyclic group is a non-aromatic, i.e. saturated or partially unsaturated, C_5-C_{10} carbocyclic ring in which one or more, for example one, two, three or four, of the carbon atoms is replaced by a heteroatom selected from O, S and N. Examples of suitable such heterocyclyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, imidazolidinyl, thiazolidinyl, 1,4-dioxanyl and 1,3-dioxolanyl.

The invention also provides the use of a compound of formula (I) for the manufacture of a medicament for use in treating a disorder mediated by histone deacetylase. In this embodiment, preferably one or two of R^1, R^2 and R^3 is/are hydrogen and the other one or two of R^1, R^2 and R^3 is/are hydrogen.

Preferably R^1, R^2 and R^3 are each independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, halo, C_1-C_6 haloalkyl, (C_1-C_6 alkoxy)carbonyl or C_1-C_6 alkyl substituted by amino, C_1-C_6 alkoxy, C_1-C_6 alkylamino or di (C_1-C_6 alkyl)amino. R^1, R^2 and R^3 may therefore be selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, chloro, fluoro, C_1-C_4 alkyl substituted by one, two or three chlorine or fluorine atoms, (C_1-C_4 alkoxy)carbonyl or C_1-C_4 alkyl substituted by amino, C_1 or C_2 alkoxy, C_1 or C_2 alkylamino or di(C_1 or C_2 alkyl)amino. R^1, R^2 and R^3 are most preferably selected from hydrogen, methyl, ethyl, methoxy, ethoxy, dimethylamino, chloro, fluoro, trifluoromethyl, difluoromethyl, fluoromethyl, methoxymethyl, ethoxymethyl, aminomethyl, methylaminomethyl or dimethylaminomethyl.

Generally, one or two of R^1, R^2 and R^3 is hydrogen. The others or other of R^1, R^2 and R^3 may be located at any position on the benzene ring. When two of R^1, R^2 and R^3 are hydrogen, the other is preferably located at the 4-position on the benzene ring.

Preferably R^4 and R^5 are each independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, C_1-C_6 haloalkyl or C_1-C_6 alkyl substituted by amino, C_1-C_6 alkoxy, C_1-C_6 alkylamino or di(C_1-C_6 alkyl)amino. R^4 and R^5 may therefore be selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, chloro, fluoro, C_1-C_4 alkyl substituted by one, two or three chlorine or fluorine atoms, or C_1-C_4 alkyl substituted by amino, C_1 or C_2 alkoxy, C_1 or C_2 alkylamino or di(C_1 or C_2 alkyl)amino. R^4 and R^5 are most preferably selected from hydrogen, methyl, ethyl, methoxy, ethoxy, chloro, fluoro, trifluoromethyl, difluoromethyl, fluoromethyl, methoxymethyl, ethoxymethyl, aminomethyl, methylaminomethyl or dimethylaminomethyl.

Generally, one or both of R^4 and R^5 is hydrogen. When one R^4 and R^5 is hydrogen, the other may be located at any position on the benzene ring.

Preferably, R^6 represents hydrogen, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, halo such as chlorine or fluorine, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 alkyl substituted by amino, C_1-C_6 alkoxy, C_1-C_6 alkylamino or di(C_1-C_6 alkyl)amino. R^6 may therefore be selected from hydrogen, halo such as chlorine or fluorine, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl substituted by one, two or three halo atoms, or C_1-C_4 alkyl substituted by amino, C_1 or C_2 alkoxy, C_1 or C_2 alkylamino or di(C_1 or C_2 alkyl)amino. R^6 may therefore be hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, trifluoromethyl, difluoromethyl, fluoromethyl, dimethylamino, methoxymethyl, ethoxymethyl, aminomethyl, methylaminomethyl or dimethylaminomethyl. Most preferably, R^6 is C_1-C_6 alkyl or C_1-C_4 alkyl and especially methyl.

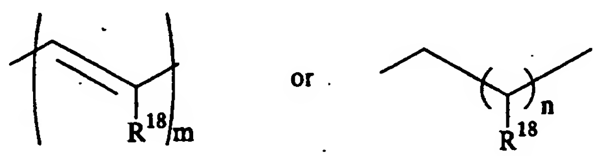
When the symbol ---- represents a single bond, R^7 and R^8 preferably each independently represent hydrogen, halo such as chloro or fluoro, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkylthio, amino, C_1-C_4 alkylamino or di(C_1-C_4 alkyl)amino. When the symbol ---- represents a double bond, R^7 is preferably hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, imidazolyl, pyrazolidinyl, oxadiazolyl, oxazyl, isoxazyl, thiadiazolyl, thiazolyl, 1,2,3-triazolyl, tetrazolyl, pyrazolyl, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} are as defined above. More preferably R^7 represents hydrogen, chloro, fluoro, C_1-C_4 alkoxy, C_1-C_4 alkoxy, C_1-C_4 alkylthio, amino, C_1-C_4 alkylamino or di(C_1-C_4 alkyl)amino. Typically, R^7 and if present R^8 each represent hydrogen.

Preferred W groups include single bond, $-C(R^{11})=N-$, $-N=C(R^{11})-$, $-C(R^{11})(R^{12})-NR^{13}-$, $-NR^{13}-C(R^{11})(R^{12})-$, $-CO-NR^{11}-$, $-NR^{11}-CO-$, $-SO_2-NR^{11}-$, $-NR^{11}-SO_2-$, $-C(R^{11})(R^{12})-O-$, $-O-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-S-$, $-S-C(R^{11})(R^{12})-$, -CO-, $-NR^{11}-$, -SO-, $-SO_2-$, S or $-[C(R^{11})R^{12}]_p-$ wherein R^{11}, R^{12} and R^{13} each independently represents hydrogen, C_1-C_6 alkyl, C_6 or C_{10} aryl or a 5 to 10-membered heterocylic group and p is an integer of from 1 to 4. More preferably W is $-C(R^{11})=N-$, $-N=C(R^{11})-$, $-C(R^{11})(R^{12})-NR^{13}-$, $-NR^{13}-C(R^{11})(R^{12})-$, $-CO-NR^{11}-$, $-NR^{11}-CO-$, $-SO_2-NR^{11}-$, $-NR^{11}-SO_2-$, $-C(R^{11})(R^{12})-O-$, $-O-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-S-$, $-S-C(R^{11})(R^{12})-$, -CO-, $-NR^{11}-$, -SO-, $-SO_2-$, S or $-[C(R^{11})R^{12}]_p-$ wherein R^{11}, R^{12} and R^{13} are as defined above.

Preferably, R^{11}, R^{12} and R^{13} are independently selected from hydrogen, methyl or ethyl. Consequently, W preferably represents a single bond, -CH=N-, -N=CH-, -CONH-, -NHCO-, $-SO_2NH-$, $NHSO_2-$, $-OCH_2-$, $-CH_2O-$, $-CH_2S-$ or $-SCH_2-$, or the equivalent groups where one or more of the hydrogen atoms are replaced with methyl or ethyl. Most preferably R^{11}, R^{12} and R^{13} are hydrogen. Particularly preferred are compounds of formula (I) in which W represents –CH=N-, -CONH-, $-SO_2NH-$, $-CH_2O$ or $-CH_2S-$. The double bonds are typically in the *trans*-configuration.

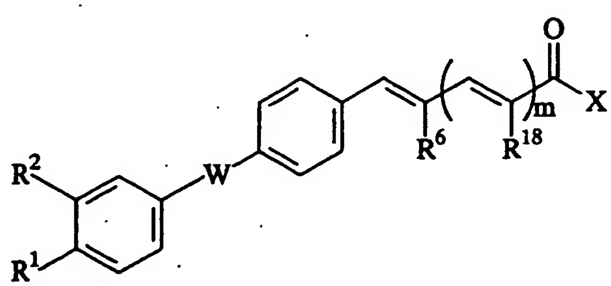
Preferably X represents $-CF_3$, $-OR^5$ or $-NHOR^5$ wherein R^5 is hydrogen or C_1-C_6 alkyl such as methyl or ethyl.

Preferably Y represents:



wherein m is 1, 2 or 3; n is 1, 2 or 3; and R^{18} is hydrogen, C_1-C_6 alkyl or C_1-C_6 alkoxy.

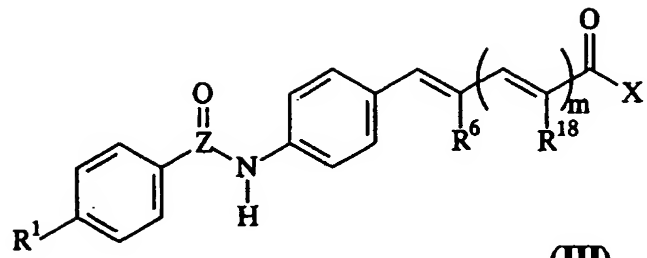
A preferred class of compounds according to the invention have the formula (II):



(II)

wherein R^1, R^2, R^6, R^{18}, W and X are as defined above and m is 1, 2 or 3; and pharmaceutically acceptable salts thereof. More especially, R^1 and R^2 each independently represent hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo or (C_1-C_6 alkoxy)carbonyl; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; W represents a single bond, -CH=N-, -N=CH-, -CONH-, -NHCO-, $-SO_2NH-$, $-NHSO_2-$, $-OCH_2-$, $-CH_2O-$, $-CH_2S-$ or $-SCH_2-$; and X represents –NHOH, $-CF_3$ or $-OR^{14}$ wherein R^{14} is hydrogen or C_1-C_4 alkyl.

More preferred are compounds having the formula (III):



(III)

wherein R^1 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halo; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; X represents –OR^{14} or –NHOH wherein R^{14} is hydrogen or C_1-C_4 alkyl; Z represents C or SO; and m is 1, 2 or 3; and pharmaceutically acceptable salts thereof. More preferably R^1 represents C_1-C_4 alkyl, C_1-C_4 alkoxy or halo.

Most preferably R^6 is hydrogen and especially methyl.

Preferred compounds of formula (III) are:

(2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)penta-2,4-dienoic acid ethyl ester;

(2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)penta-2,4-dienoic acid ethyl ester;

(2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester;

(2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid;

(2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester;

(2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-2,4-dimethylpenta-2,4-dienoic acid ethyl ester;

(2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid;

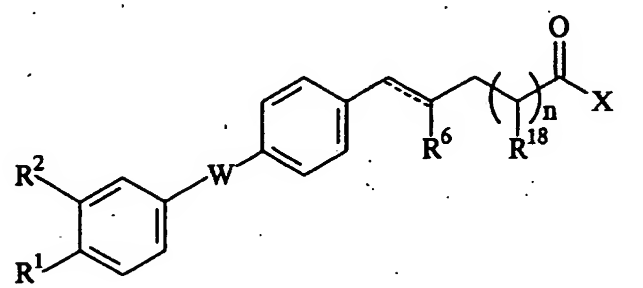
(2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester;

(2*E*,4*E*)-5-(4-methoxybenzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid hydroxamide;

(2*E*,4*E*,6*E*)-7-(4-(4-methoxybenzenesulfonylamino)phenyl)-6-methylhepta-2,4,6-trienoic acid ethyl ester; and

(2E,4E,6E)-7-(4-(4-chlorobenzoylamino)phenyl)hepta-2,4,6-trienoic acid methyl ester.

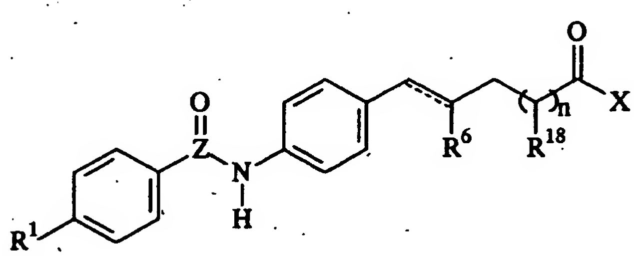
Another preferred class of compounds according to the invention have the formula (IV):



(IV)

wherein R^1, R^2, R^6, R^{18}, W and X are as defined above, the symbol ----- represents a single bond or a double bond and n is 1, 2 or 3; and pharmaceutically acceptable salts thereof. More especially, R^1 and R^2 each independently represent hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo or (C_1-C_6 alkoxy)carbonyl; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; W represents a single bond, -CH=N-, -N=CH-, -CONH-, -NHCO-, $-SO_2NH-$, $-NHSO_2-$. $-OCH_2-$, $-CH_2O-$, $-CH_2S-$ or $-SCH_2-$; and X represents -NHOH, $-CF_3$ or $-OR^{14}$ wherein R^{14} is hydrogen or C_1-C_4 alkyl.

More preferred are compounds which have the formula (V):



(V)

wherein the symbol ----- represents a single bond or a double bond; R^1 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halo; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; X represents $-OR^{14}$ or $-NHOH$ wherein R^{14} is hydrogen or C_1-C_4 alkyl; Z represents C or SO; and n is 1, 2 or 3; and pharmaceutically acceptable salts thereof. More preferably R^1 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halo. Preferably R^6 is hydrogen and especially methyl.

Preferred compounds of formula (V) are:

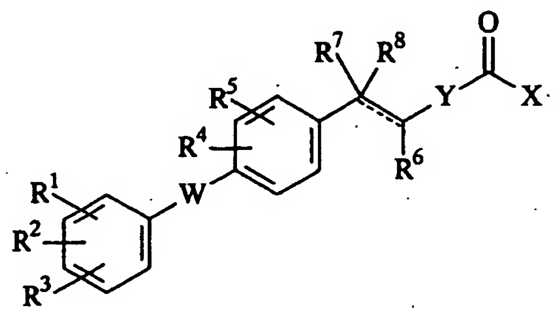
5-[4-(4-methoxybenzenesulfonylamino)phenyl]-4-methylpentanoic acid ethyl ester;

ethyl 5-[4-(4-chlorobenzoylamino)phenyl]-4-methylpentanoate;

ethyl 5-[4-(4-chlorobenzoylamino)phenyl]-4-methylpentanoate;

5-[4-(4-chlorobenzenesulfonylamino)phenyl]-4-methylpentanoic acid hydroxyamide; and 5-[4-(4-chlorobenzoylamino)phenyl]-4-methylpentanoic acid hydroxyamide.

The invention also provides compounds of formula (VI):



(VI)

wherein

- the symbol ---- represents a single bond or a double bond or the symbol ----, R^6 and R^8 together represent cyclopropyl;

- R^1 to R^5 each independently represent hydrogen, C_2-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, C_1-C_{10} hydroxyalkyl, halo, C_1-C_{10} haloalkyl, amino, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amido, nitro, cyano, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, (C_1-C_{10} alkyl)sulfinyl, (C_1-C_{10} alkyl)sulfonyl or C_1-C_{10} alkyl substituted by amino, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino or di(C_1-C_{10} alkyl)amino;

- R^6 represents hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, an unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double or triple bond, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, halo, cyano, nitro, amino, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amido, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, (C_1-C_{10} alkyl)sulfinyl, (C_1-C_{10} alkyl)sulfonyl, a saturated or unsaturated C_3-C_{12} hydrocarbon chain interrupted by O, S, NR, CO, C=NR, N(R)SO_2, SO_2N(R), N(R)C(O)O, OC(O)N(R), N(R)C(O)N(R), OC(O), C(O)O, OSO_2, SO_2O or OC(O)O where:

(a) R independently represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, hydroxyl or C_1-C_{10} haloalkyl, and

(b) the saturated or unsaturated hydrocarbon chain is optionally substituted with C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, hydroxyl, C_1-C_{10} hydroxyalkyl, halo, C_1-C_{10} haloalkyl, amino, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl or C_1-C_{10} alkylsulfonyl,

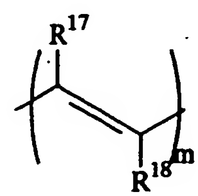
- when the symbol ---- represents a single bond, R^7 and R^8 each independently represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} each independently represent hydrogen or C_1-C_6 alkyl or one of R^9 and R^{10} is H and the other is –CO(C_1-C_6 alkyl). or R^7 and R^8 together represent =O, =CH_2 or =CHR^9 wherein R^9 is as defined above;

- when the symbol ---- represents a double bond, R^7 represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} are as defined above and R^8 is absent;

- W represents a single bond, -C(R^{11})=N-, -N=C(R^{11})-, -C(R^{11})(R^{12})-NR^{13}-, -NR^{13}-C(R^{11})(R^{12})-, -CO-NR^{11}-, -NR^{11}-CO-, -SO_2-NR^{11}-, -NR^{11}-SO_2-, -C(R^{11})(R^{12})-O-, -O-C(R^{11})(R^{12})-, –C(R^{11})(R^{12})-S-, -S-C(R^{11})(R^{12})-, -CO-, -NR^{11}-, -SO-, -SO_2-, S or –$[C(R^{11})R^{12}]_p$- wherein R^{11}, R^{12} and R^{13} each independently represents hydrogen, C_1-C_6 alkyl, C_6 or C_{10} aryl or a 5- to 10- membered heterocyclic group alkyl and p is an integer of from 1 to 4;

- X represents –OR^{14}, -SR^{14}, -$NR^{14}OR^{15}$,–$NR^{14}NR^{15}R^{16}$, -CF_3, -CF_2H or CH_2F wherein R^{14}, R^{15} and R^{16} each independently represents hydrogen or C_1-C_6 alkyl; and

- Y represents



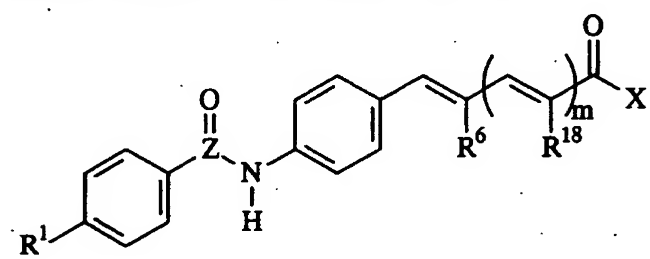
wherein m is an integer from 1 to 4; n is an integer from 1 to 8; and R^{17} and R^{18} each independently represents hydrogen, unsubstituted or substituted C_1-C_{10} alkyl, an unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double and/or triple bonds, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, halo, cyano, nitro, amino, amido, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10}

alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, C_1-C_{10} alkylsulfinyl, C_1-C_{10} alkylsulfonyl, or a saturated or unsaturated C_3-C_{12} hydrocarbon chain interrupted by O, S, NR, CO, C(NR), N(R)SO_2, SO_2N(R), N(R)C(O)O, OC(O)N(R), N(R)C(O)N(R), OC(O), C(O)O, OSO_2, SO_2O or OC(O)O where R is as defined above and the saturated or unsaturated hydrocarbon chain is optionally substituted as defined above;

and pharmaceutically acceptable salts thereof.

Preferred features of the compounds of formula (VI) are as previously defined for the compounds of formula (I). In particular, it is preferred that R^1, R^2 and R^3 are selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, halo, C_1-C_6 haloalkyl, (C_1-C_6 alkoxy)carbonyl or C_1-C_6 alkyl substituted by amino, C_1-C_6 alkoxy, C_1-C_6 alkylamino or di(C_1-C_6 alkyl) amino. More preferably one or two of R^1, R^2 and R^3 is hydrogen.

Preferred compounds of formula (VI) are those of formula (VII):



(VII)

wherein R^1 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halo; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; X represents $-OR^{14}$ or –NHOH wherein R^{14} is hydrogen or C_1-C_4 alkyl; Z represents C or SO; and m is 1, 2 or 3; and pharmaceutically acceptable salts thereof. More preferably R^6 is methyl.

The preferred compounds of formula (VI) include:

(2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester;

(2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid; and

(2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid hydroxamide.

The compounds of formula (VI) can also be used in the manufacture of medicaments for use in the treatment of a disorder mediated by histone deacetylase.

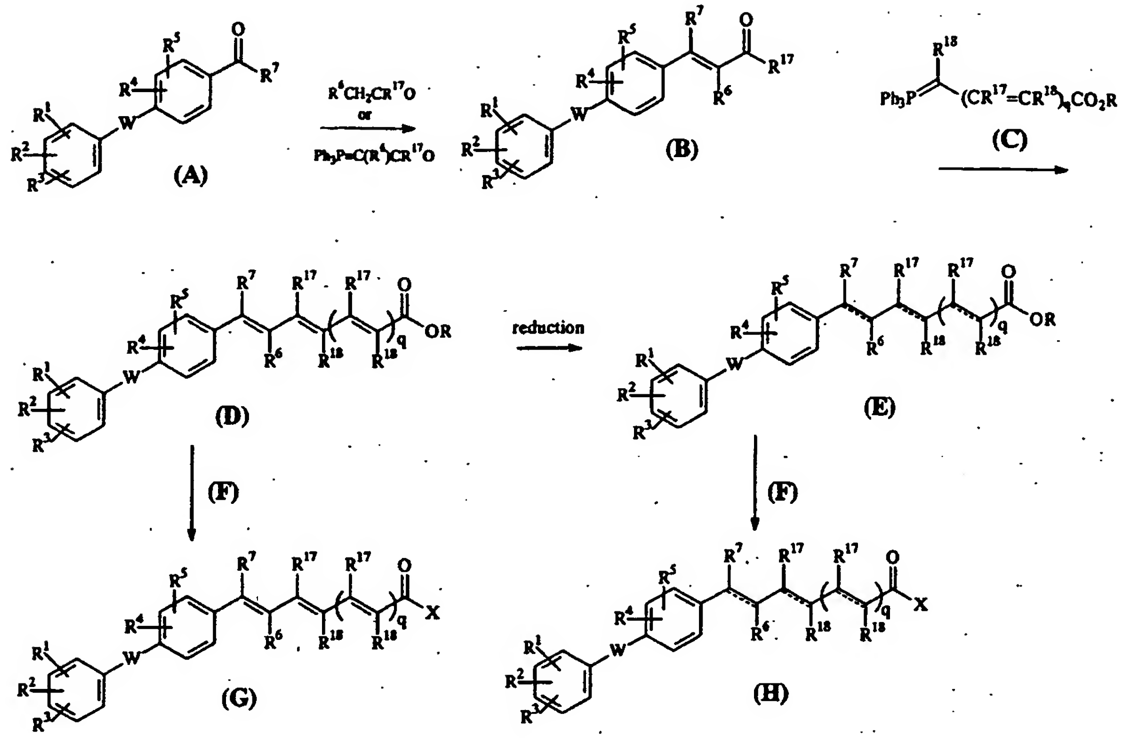
As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric,

hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium), alkali earth metal (e.g. calcium or magnesium), zinc and iron hydroxides and organic bases such as C_1-C_6 alkyl amines, aralkyl amines or heterocyclic amines. An example of a primary amine salt can be the cyclohexylammonium salt, a suitable secondary amine salt may be the piperidine salt and a tertiary amine salt may be the triethylamine salt.

Tautomers of compounds of formula (I) and (VI) also form part of the invention. Also, the compounds of the invention can contain one or more chiral centre. For the avoidance of doubt, the chemical structures depicted herein are intended to embrace all stereoisomers of the compounds shown, including racemic and non-racemic mixtures and pure enantiomers and/or diastereoisomers. Preferred compounds of the invention are optically active isomers. Thus, for example, preferred compounds of formula (I) containing only one chiral centre include an R enantiomer in substantially pure form, an S enantiomer in substantially pure form and enantiomeric mixtures which contain an excess of the R enantiomer or an excess of the S enantiomer.

The compounds of formula (I) and (VI) and their salts may be prepared by adaptation of conventional procedures. For example, Scheme 1 below illustrates one way in which compounds of the invention may be prepared. The compounds thus prepared can then be converted as desired into pharmaceutically acceptable salts by conventional routes. In all Schemes and in the Examples, the benzene ring and the chain incorporating the group Y which are either side of the symbol $\overline{}$ shown in formula (I) are in the *trans* configuration with respect to each other when the symbol $\overline{}$ represents a carbon-carbon double bond. Compounds in which the symbol $\overline{}$ represents a carbon-carbon double bond therefore are isolated as the *trans*-isomer, *trans-trans*-isomer, *trans-trans-trans*-isomer, etc.

Scheme 1



In the starting material (A), R^1 to R^5, R^7 and W are as defined above. Typically R^7 represents hydrogen. Compound (A) can be obtained by a variety of methods, depending on the nature of W. Thus:

- When W represents a single bond, one of the following will typically be used: Suzuki coupling (of a boronic acid or ester with an aryl halide or triflate), Ullman coupling (copper-catalysed coupling of aryl halides or related compounds), Gomberg reaction (arylation of diazonium salts) or other metal-catalysed aryl-aryl coupling of aryl halides, triflates or related compounds.

- When W represents an imine of formula $-N{=}C(R^{11})-$ or $-C(R^{11}){=}N-$, compound (A) may be prepared from an arylamine of formula $Ar-NHR^{11}$ and an aromatic aldehyde or ketone. When R^{11} is OH, W in the resulting compound of formula (A) will exist as the amide group of formula $-N(R^{11})C(O)-$ or $-C(O)NR^{11}-$, rather than as the corresponding hydroxyimine, due to keto-enol tautomerism.

- When W represents -$C(R^{11})(R^{12})$-NR^{13}- or –NR^{13}-$C(R^{11})(R^{12})$-, compound (A) may be prepared by reduction of the corresponding imine or amide using hydrogen and a catalyst or a metal hydride system, or by addition of an organometallic reagent to the imine preceded and followed by suitable protection and deprotection respectively of the ketone group present in (A). A preferred method of preparing such compounds (A) is by reaction of a suitable amine with a suitable aldehyde or ketone under reductive conditions, using reagents such as sodium cyanoborohydride or sodium triacetoxyborohydride.

- When W represents -NR^{11}-CO- or –CO-NR^{11}-, compound (A) may be prepared by reaction of ArCOQ (wherein Q is a leaving group, typically Cl) with an arylamine in the presence of a base.

- When W represents CO, Friedel-Crafts arylation or metal-catalysed coupling involving ArCOQ compounds are preferred (wherein Q is a leaving group, typically Cl).

- When W represents -SO_2-NR^{11}- or –$R^{11}N$-SO_2-, compound (A) may be prepared by sulfonylation (typically using $ArSO_2Cl$) of an arylamine in the presence of a base.

- When W represents -$[C(R^{11})R^{12}]_p$-, compound (A) may be prepared by a Friedel-Crafts procedure (especially when R^{11} and R^{12} are both hydrogen) followed by reduction (hydrogen and a catalyst) or N_2H_4-KOH (Wolf-Kishner) or related procedures.

- For an alkyl chain in W, a Wittig reaction followed by reduction, typically using hydrogen and a catalyst, is the preferred method.

- When W represents -NR^{11}-, compound (A) may be prepared by catalytic amination of an aryl halide, typically with a palladium-based catalyst, although displacement of an aryl halide or triflate by an arylamine or metal salt may also be used.

- When W represents O, compound (A) may be prepared by etherification of an aryl halide or triflate with a phenol, or more preferably its metal salt, typically in the presence of a metal catalyst such as a copper, palladium or nickel derivative or the metal itself.

- When W represents S, compound (A) may be prepared by displacement of an aryl halide or triflate, with a thiophenol. This may be in the presence of a metal catalyst or more preferably a metal salt of the thiophenol. Alternatively, the metal salt of the thiophenol may also be reacted with a diazonium salt.

- When W represents SO, compound (A) may be prepared by oxidation of the corresponding compound (A) where W represents S with hydrogen peroxide or $NaIO_4$.

- When W represents SO_2, compound (A) may be prepared by oxidation with H_2O_2 or $NaIO_4$ of the corresponding compound (A) where W represents S with a peracid, typically *m*-chloroperoxybenzoic acid, or by oxidation of the corresponding compound (A) where W represents SO with $NaIO_4$.

- When W represents $-O-C(R^{11})(R^{12})-$ or $-C(R^{11})(R^{12})-O-$, compound (A) may be prepared by a Williamson ether-type synthesis involving a phenol or more preferably its metal salt with an alkyl halide, triflate or related displaceable group, i.e. $ArC(R^{11})(R^{12})Q$, wherein Q is a leaving group, typically halogen or triflate, preferably Br.

- When W represents $-S-C(R^{11})(R^{12})-$ or $-C(R^{11})(R^{12})-S-$, compound (A) may be prepared by reaction of a thiophenol or more preferably its metal salt with an alkyl halide [$ArC(R^{11})(R^{12})Q$ (wherein Q is a leaving group, typically halogen or triflate, preferably Br].

In Scheme 1, compound (A) is reacted with either an aldehyde $R^6CH_2CR^{17}O$, typically in the presence of an acidic or basic catalyst, or a Wittig or related reagent such as $PH_3P{=}C(R^6)CR^{17}O$. R^{17} is preferably H, CH_3 or CH_2CH_3. More preferably, R^{17} is H or Me. Typically, R^{17} is H. The aromatic ring and the $-C(O)R^{17}$ moiety are typically *trans* with respect to each other in the resulting compound (B).

Compound (B) is then reacted with compound (C) to form compound (D). (C) is typically either a Wittig or related reagent of type $Ph_3P{=}C(R^{18})(CR^{17}{=}CR^{18})_qCO_2R$ wherein q = 0, 1, 2 or 3 and R^{17} and R^{18} are each independently as defined above. Preferably R^{17} and R^{18} are independently selected from H, CH_3 and CH_2CH_3. More preferably, they are H or CH_3 and typically both denote H. Within any $(CR^{17}{=}CR^{18})$ moiety, it is preferred that one of R^{17} and R^{18} is H. The other may be CH_3 but typically both R_{17} and R_{18} are H. The group R in compound (C) is hydrogen or C_1-C_{10} alkyl. Preferably R is H, CH_3 or CH_2CH_3. When R is H, reaction of the acid group to form the corresponding methyl or ethyl ester is typically carried out before reaction with (B).

A reduction is carried out to convert compound (D) to compound (E). One, two or more of the carbon-carbon double bonds in the chain of compound (D), for example all such bonds, are thus reduced to single bonds. Where saturation of all such double bonds is desired, excess hydrogen and a metal catalyst such as Pd or

palladium-on-carbon may be used. Where partial saturation is desired, suitable reagents are (a) Mg/ROH wherein R is C_1-C_{10} alkyl or (b) R_3SiH/H^+.

The partial reduction can be carried out selectively. Thus, where the double bond adjacent to the –COOR group of compound (D) is to be hydrogenated, a magnesium or related metal, together with an alcohol, typically methanol or ethanol, can be used. Where at least one of the double bonds that is not adjacent to the –COOR group of compound (D) is to be hydrogenated, a trialkylsilane or related agent, together with an acid, can be used. The desired degree of saturation may alternatively be incorporated from the Wittig reagent as appropriate.

Where the compound (G) is desired, compound (D) is reacted with reagent (F). In an analogous fashion, compound (H) is formed by reaction of compound (E) with reagent (F). The nature of reagent (F) is dependent on the nature of the desired group X of compound (G) or (H). Suitable methods for forming the group X as are follows.

For X = NHOH, this is typically achieved by reaction of the methyl or ethyl ester of (D) or (E) with aqueous hydroxylamine. A compound (G) or (H) in which X = OH can be obtained by alkaline hydrolysis of an ester (D) or (E) with sodium or potassium hydroxide (or other alkali or related metal hydroxide) followed by acidification. When it is wished to form a compound (G) or (H) in which X = CF_3, a carboxylic acid (D) or (E) can be reacted with (i) oxalyl chloride, (ii) $(CF_3CO)_2O$ and pyridine, and then (iii) water.

A compound (G) or (H) in which X= CH_2F is typically obtained by alkaline hydrolysis of an ester (D) or (E) with sodium or potassium hydroxide (or other alkali or related metal hydroxide) followed by acidification and treatment of the carboxylic acid so obtained with (i) $ClCO_2$i-Bu and N-methyl-morpholine, (ii) CH_2N_2 and Et_3N and (iii) HBr and AcOH to give the corresponding bromomethyl ketone. That ketone is then converted into the corresponding fluoromethyl ketone using KF and 18-crown-6 in acetonitrile.

When it is wished to form a compound (G) or (H) in which X = CHF_2, this is typically achieved by alkaline hydrolysis of an ester (D) or (E) with sodium or potassium hydroxide (or other alkali or related metal hydroxide) followed by acidification and treatment of the carboxylic acid so obtained with $EtOC(O)CHF_2$. A compound (G) or (H) in which X = SR^{14} can be prepared by reaction of an ester (D) or (E) with a metal salt of a thiol having a SR^{14} group. A compound (G) or (H) in which X

$= NR^{14}OR^{15}$ is obtainable by reaction of an ester (D) or (E) with $HNR^{14}OR^{15}$. A compound (G) or (H) in which X = $-NR^{14}NR^{15}R^{16}$ can be formed by reaction of an ester (D) or (E) with $NHR^{14}NR^{15}R^{16}$. Alternatively such a compound can be obtained by reaction of the corresponding carboxylic acid (obtainable from the ester as described above for X=OH) with an activating reagent such as iso-butyl chloroformate or DCC, followed by the addition of $HNR^{14}NR^{15}R^{16}$.

For compounds containing a cyclopropyl ring, the preferred preparation method includes reduction of (B) to the corresponding alcohol using hydrogen and a metal catalyst or using a metal-hydride system. Cyclopropanation is then effected with an iodoorganozinc reagent. Where an enantio-enriched product is required, a chiral co-reagent such as a dialkyl tartrate or dialkyl tartramide is added, and subsequent oxidation (back to the aldehyde) to form the derivative of (B) that has the structure $ArCR^7(CH_2)CR^6CHO$. This can then be reacted further, as described above. The cyclopropyl ring may alternatively be introduced by cyclopropanation of more unsaturated systems, such as compound (D), by a variety of reagents including CH_2I_2 with a zinc-copper couple.

In a variation of Scheme 1, compound (A) or compound (B) may be reacted with a Wittig reagent of the type $Ph_3P=C(R')(CH_2)_nCOOR$ where R' is typically H, R is typically CH_3 or CH_2CH_3 and n is as defined above. In this way, compound (E) and like saturated ester derivatives can be prepared.

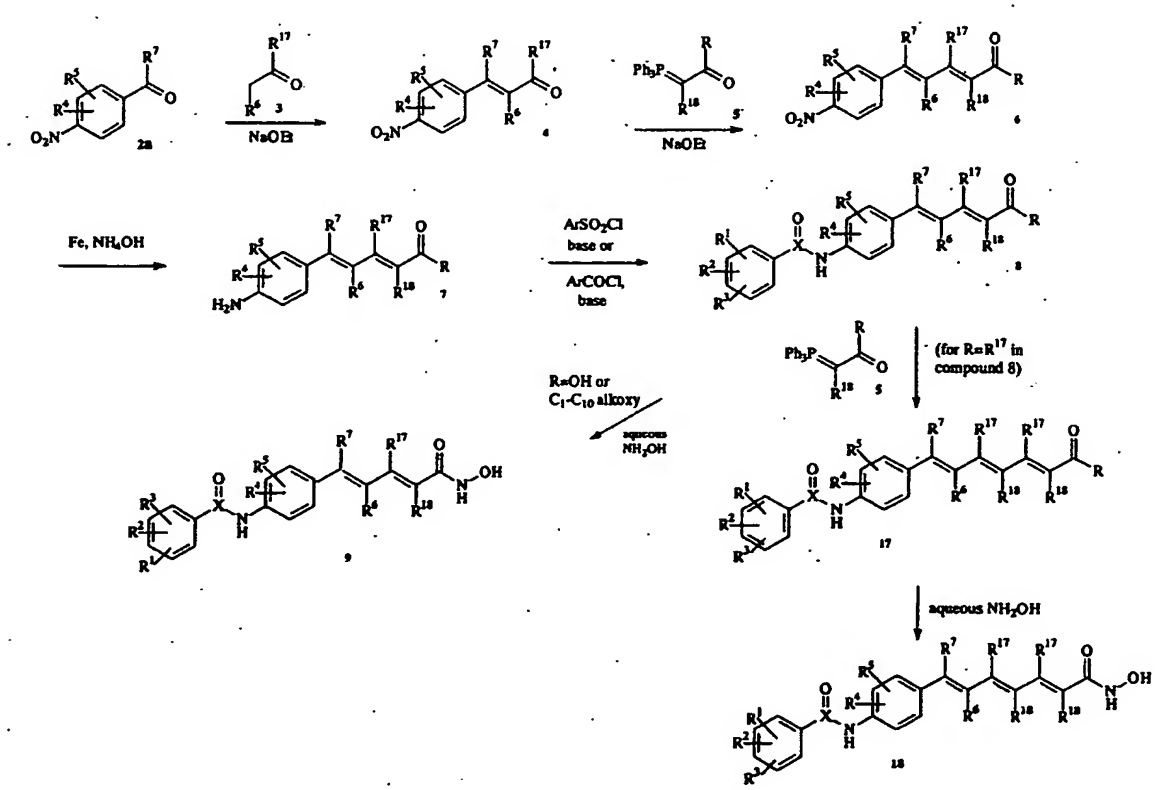
When W represents $-CONR^{11}-$ or $-S(O)NR^{11}-$, the Ar group in $Ar\text{-}W\text{-}C_6H_2(R^4)(R^5)CHO$ can attached later in another variation of Scheme 1. Thus, a *p*-nitrobenzaldehyde replaces compound (A) and is reacted with $R^6CH_2CR^{17}O$ or $Ph_3P=C(R^6)CR^{17}O$. The product may then be reacted with compound (C) to give a nitro ester that is reduced, preferably with Fe and aqueous ammonia, to convert the $-NO_2$ group into an $-NH_2$ group, that amine then being reacted with an acid chloride or sulfonyl chloride to give a compound of formula (D) or a compound of formula (E).

When R_7 and R_8 together represent =O (i.e. a ketone group) in a compound of formula (I), a variant procedure typically involves the addition of an organometallic reagent such as $XZn(CH_2)_nCO_2R$ wherein X is halogen, typically Br or I, to compound (A) where R^7=H to give the corresponding alcohol. That alcohol is then oxidised (e.g. with MnO_2 or chromium (IV) reagent or oxygen or air and a metal catalyst, or other oxidising reagent) to give a compound of formula (I) (typically where Y is a saturated

chain). This ketone of formula (I) may be converted into the alkene using $Ph_3P{=}CHR^9$ or a related reagent.

Schemes 2 to 5 shown below illustrate syntheses for producing certain aspects of the invention, for example when R^1, R^2, R^3, R^4 and R^5 are selected from H, C_1-C_{10} alkyl and C_1-C_{10} alkoxy. Where they appear in Schemes 2 to 5, R^{17} and R^{18} are independently defined as above. Preferably, R^{17} and R^{18} are independently H, CH_3 or CH_2CH_3. Typically, they are H. Within any ($CR^{17}{=}CR^{18}$) moiety, it is preferred that one or R^{17} and R^{18} is H and the other is CH_3. More preferably, both are H. Unless stated otherwise, other substituents are defined as above.

Scheme 2

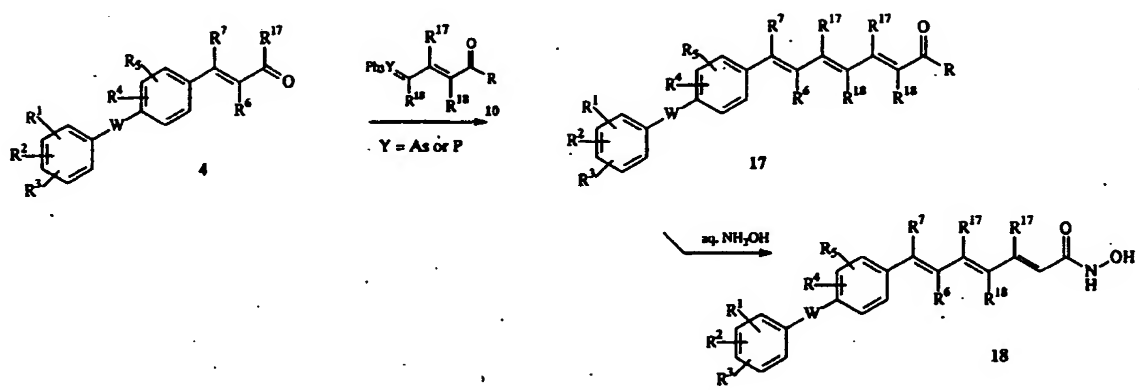


In Scheme 2, a route is shown to carboxylic acids (**8**) and their ester derivatives, and also their hydroxamic acid derivatives (**9**). An aldol or related condensation, typically initiated by base though acid and other catalysts or reagents are feasible, is followed by dehydration to give the unsaturated aldehydes (**4**) which undergo a Wittig

or related process to afford the dienic carbonyl compounds (6). Here, a related process includes Horner-Wadsworth-Emmon's or other modifications, as well as compounds other than (5) (*e.g.* simple or complex enolates, or enolate equivalents of an appropriate carbonyl compound, such as enamino esters, enamino ketones or metal complexes derived from α-halo esters and related compounds). The group R of (5) is typically hydroxy or C_1-C_{10} alkoxy such as, in particular, $-OCH_3$ or $-OCH_2CH_3$.

Reduction of the nitro group of (6) to the amino derivative (7) can be carried out by many reagents, but iron and aqueous ammonia mixtures are shown to be particularly effective and convenient. *N*-Sulfonylation and *N*-acylation of (7) affords the corresponding respective sulfonamides and esters (8). Such sulfonylations are typically carried out with an arenesulfonyl chloride and base, and the corresponding acylations with an acid chloride and a base. Many bases may possibly be employed. However, use of pyridine or a related base or of an aliphatic tertiary amine is preferred. In some cases, alkali metal hydroxides may suffice.

Scheme 3

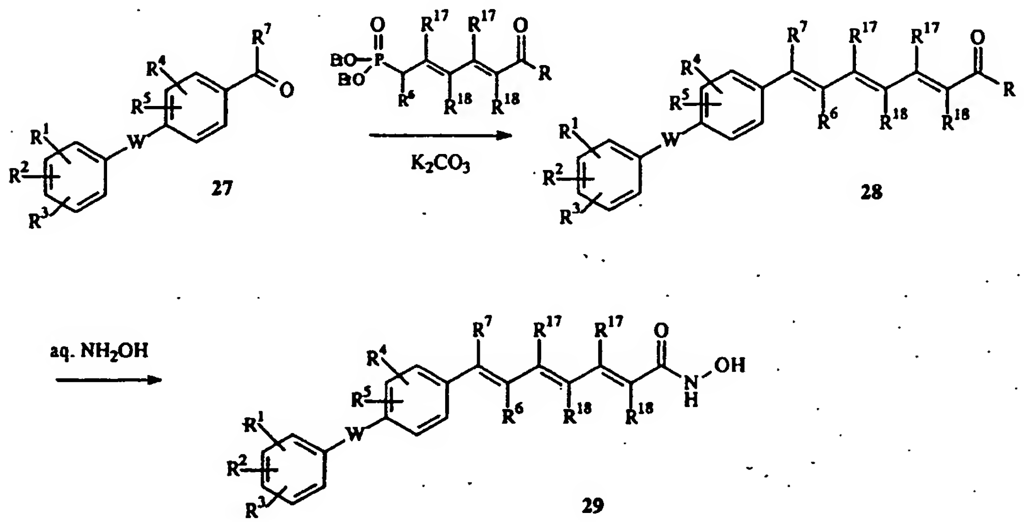


Scheme 3 shows a route to carboxylic acids (17) and their ester derivatives, and also to the hydroxamic acid derivatives (18). The unsaturated aldehydes (4) undergo a Wittig or related process to afford the trienic carbonyl compounds (17). Here, a related process includes Horner-Wadsworth-Emmons or other modifications, as well as use of compounds other than phosphorus or arsenic ylid (10) (*e.g.* simple or complex enolates, or enolate equivalents of an appropriate carbonyl compound, such as enamino esters, enamino ketones or metal complexes derived from α-halo esters and related compounds). The trienic carbonyl compound (17) so obtained can then be converted

into other derivatives, but preferably the hydroxamic acids (18). The phosphorus or arsenic ylid may have a variety of substituents (*e.g.* trialkyl or unsymmetrical alkyl and/or aryl substituents) and is not intended to be limited to Ph_3P- or Ph_3As- as shown in the Scheme.

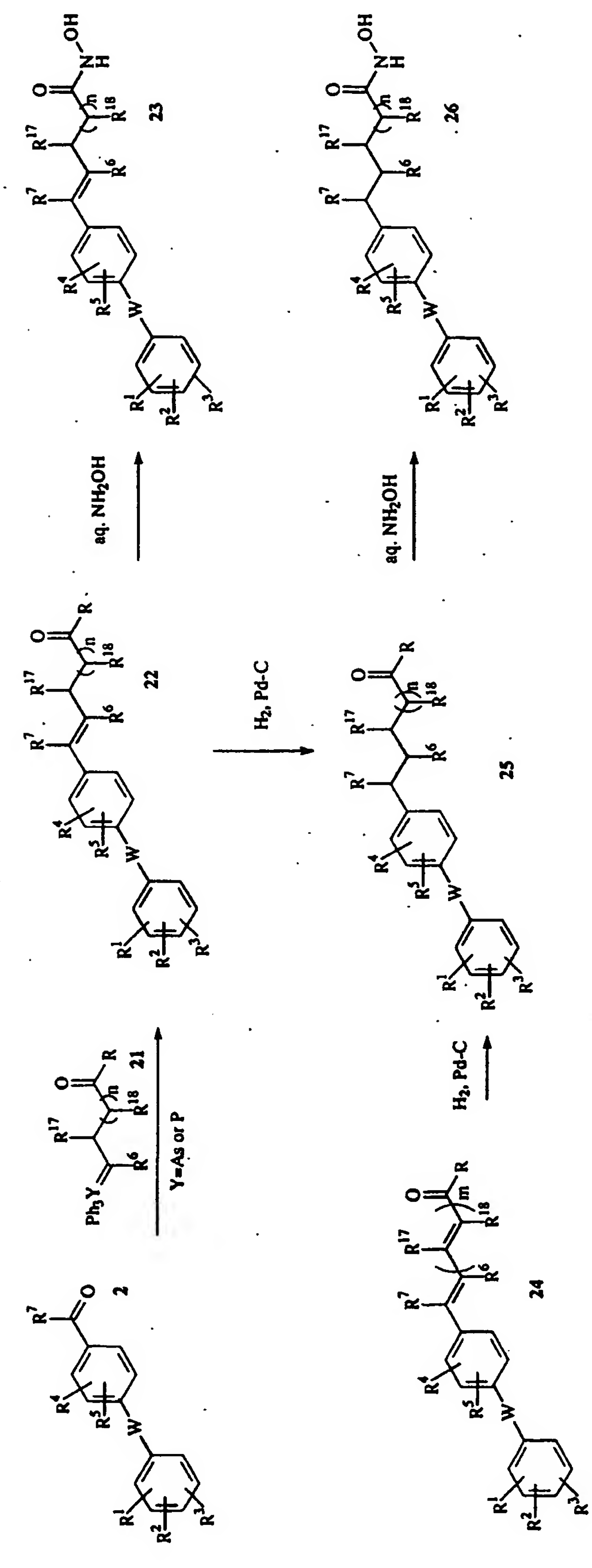
The group R of the phosphorus or arsenic ylid (10) and of compound (17) is hydroxy or C_1-C_{10} alkoxy. Preferably, R is C_1-C_{10} alkoxy. Typically, it is $-OCH_3$ or $-OCH_2CH_3$. When it is desired that R should denote hydroxy in compound (17), this may be achieved by hydrolysis of the corresponding ester compound (17) in which R is C_1-C_{10} alkoxy. If R denotes hydroxy in compound (17), the reaction of (17) to (18) may require activation of the acid group of compound (17).

Scheme 4



In Scheme 4, a route is shown to carboxylic acids and their ester derivatives (28) and also their hydroxamic acid derivatives (29) via a Horner-Wadsworth-Emmons reaction. The phosphorus ylid reagent provides the group Y shown in formula (I). In this case, the ylid provides a $-CR^{17}$=CR^{18}-CR^{17}=CR^{18}- group. The group R in Scheme 4 is generally hydroxy or C_1-C_{10} alkoxy.

Scheme 5



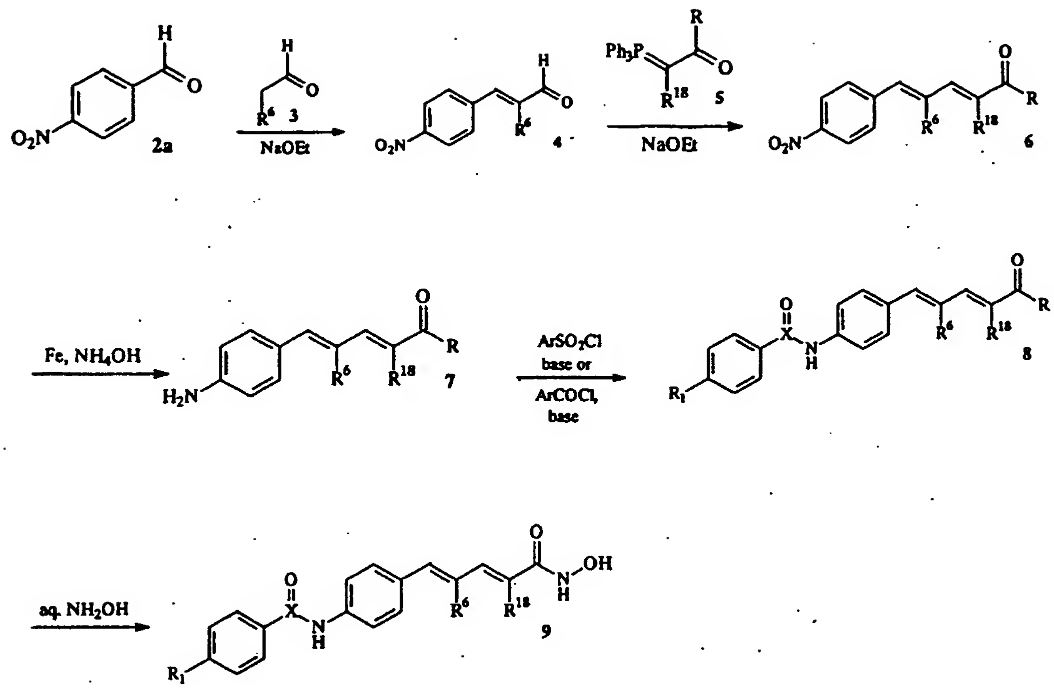
In Scheme 5 are shown routes to carboxylic acids (22) and (25) and their ester derivatives, and also their hydroxamic acid derivatives (23) and (26). A Wittig or related process affords the carbonyl compounds (22). Here, a related process includes Horner-Wadsworth-Emmons or other modifications, and also the analogous arsenic ylids, as well as compounds other than the phosphorus or arsenic ylid (21) (*e.g.* simple or complex enolates, or enolate equivalents of an appropriate carbonyl compound, such as enamino esters, enamino ketones or metal complexes derived from α-halo esters and related compounds).

The carbonyl compound (22) so obtained can then be converted into other derivatives, but especially the hydroxamic acids (23). The phosphorus or arsenic ylid may have a variety of substituents (*e.g.* trialkyl or unsymmetrical alkyl and/or aryl substituents) and is not intended to be limited to Ph_3P- or Ph_3As- as shown in the Scheme. The carbonyl compounds (22) can also be reduced, typically with hydrogen and a catalyst(s) (*e.g.* Pd, Ni, Co *etc.*) or by hydrosilylation or hydride-acid systems and other processes to give the carboxylic acids (25) and their derivatives. In particular, the ester derivatives (22) and (25) can be converted, typically by aqueous hydroxylamine, but also by hydroxylamine derivatives with or without bases, respectively into the hydroxamic acids (23) and (26).

The group R in compounds (21) and (24) is typically hydroxy or C_1-C_{10} alkoxy. Preferably, R is C_1-C_{10} alkoxy and especially is $-OCH_3$ or $-OCH_2CH_3$. When R=OH is desired in compound (22), this may be achieved by standard methods of hydrolysis of the corresponding ester compound (22) formed when R is C_1-C_{10} alkoxy in compound (21). If R is OH, the reaction of (22) to (23) and (25) to (26) may require activation of the acid group of compound (22) or (25) respectively.

Preferred reaction procedures are set out in Schemes 6 to 9 shown below. In Schemes 6 to 9, the symbols shown in the formulae are as defined above unless otherwise indicated.

Scheme 6

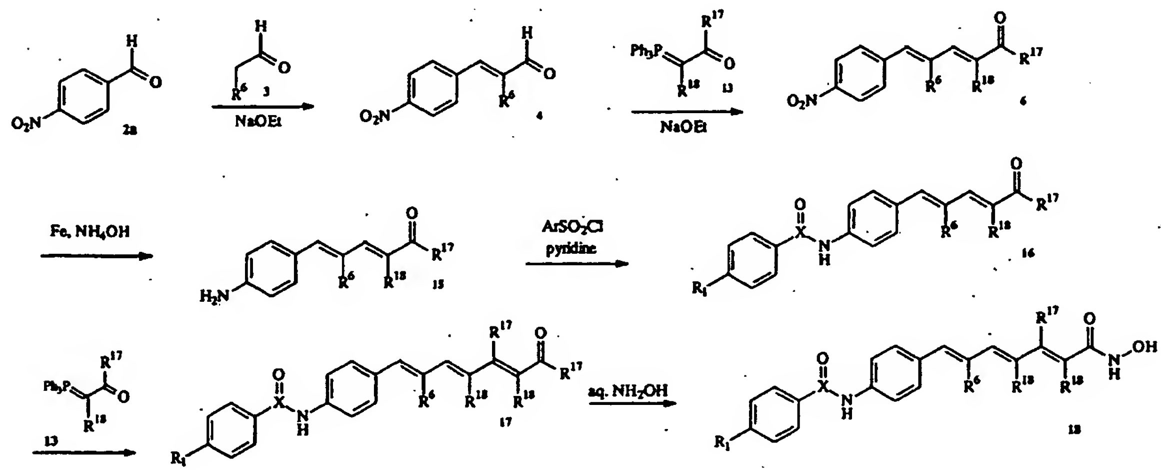


In Scheme 6 is shown a route to carboxylic acids (8) and their ester derivatives, and also their hydroxamic acid derivatives (9). An aldol or related condensation, typically initiated by base though acid and other catalysts or reagents being feasible, is followed by dehydration to give the unsaturated aldehydes (4) which undergo a Wittig or related process to afford the dienic carbonyl compounds (6). Here, a related process includes Horner-Wadsworth-Emmons or other modifications, as well as compounds other than (5) (*e.g.* simple or complex enolates, or enolate equivalents of an appropriate carbonyl compound, such as enamino esters, enamino ketones or metal complexes derived from α-halo esters and related compounds). The group R of reagent (5) is typically hydroxy or C_1-C_{10} alkoxy such as, in particular, $-OCH_3$ or $-OCH_2CH_3$.

Reduction of the nitro group of (6) to the amino derivative (7) can be carried out be many reagents, but iron and aqueous ammonia mixtures are shown to be particularly effective and convenient. *N*-Sulfonylation and *N*-acylation of (7) affords the corresponding respective sulfonamides and esters (8) in which X is C or SO. Such sulfonylations are typically carried out with an arenesulfonyl chloride and base, and the

corresponding acylations with an acid chloride and a base. Many bases may possibly be employed. However, use of pyridine or a related base or of an aliphatic tertiary amine is preferred. In some cases, alkali metal hydroxides may suffice.

Scheme 7

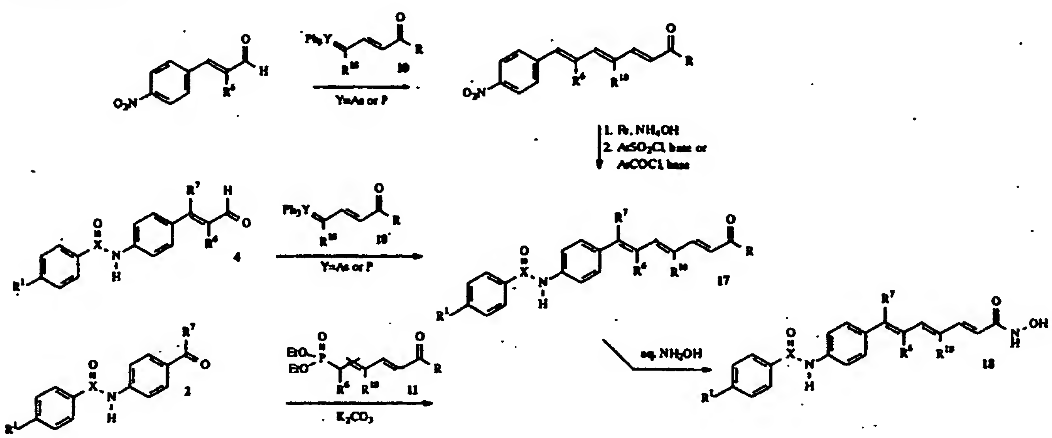


Scheme 7 is similar to Scheme 6. Scheme 7 provides a route to carboxylic acids (17) and their ester derivatives, and also their hydroxamic acid derivatives (18). An aldol or related condensation, typically initiated by base but acid and other catalysts or reagents are feasible, is followed by dehydration to give the unsaturated aldehydes (4) which undergo a Wittig or related process to afford the dienic carbonyl compounds (6). Here, a related process includes Horner-Wadsworth-Emmons or other modifications, as well as use of compounds other than the phosphorus ylid (13) (*e.g.* simple or complex enolates, or enolate equivalents of an appropriate carbonyl compound, such as enamino esters, enamino ketones or metal complexes derived from α-halo esters and related compounds). The group R in the phosphorus ylid (13) is typically hydroxy or C_1-C_{10} alkoxy. Preferably, R is C_1-C_{10} alkoxy and especially $-OCH_3$ or $-OCH_2CH_3$.

Reduction of the nitro group of compound (6) to the amino derivative (15) can be carried out be many reagents, but iron and aqueous ammonia mixtures are particularly effective and convenient. *N*-Sulfonylation and *N*-acylation of (15) affords the corresponding respective sulfonamides and esters (16) in which X is C or SO. Such sulfonylations are typically carried out with an arenesulfonyl chloride and base, and the corresponding acylations with an acid chloride and a base. Many bases may possibly be

employed. However, use of pyridine or a related base or of an aliphatic tertiary amine is preferred although in some cases alkali metal hydroxides may suffice.

Scheme 8



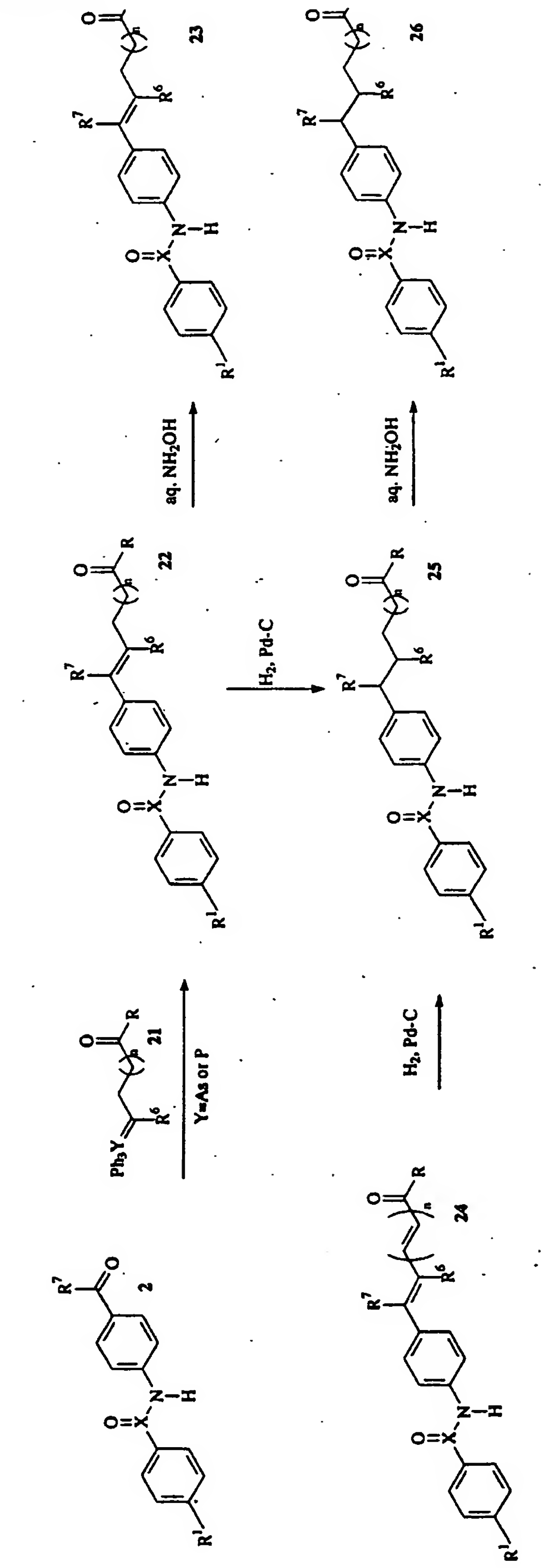
Scheme 8 provides an alternative route to carboxylic acids (17) and their ester derivatives, and also their hydroxamic acid derivatives (18). The group X denotes C or SO. A Wittig or related process affords the trienic compounds (17). Here, a related process includes Horner-Wadsworth-Emmons or other modifications, and also use of analogous arsenic ylides as well as use of compounds other than (10) and (11) (*e.g.* simple or complex enolates, or enolate equivalents of an appropriate carbonyl compound, such as enamino esters, enamino ketones or metal complexes derived from α-halo esters and related compounds). The group R in reagents (10) and (11) is typically hydroxy or C_1-C_{10} alkoxy and especially $-OCH_3$ or $-OCH_2CH_3$.

The trienic compound (17) can be converted into other compounds of formula (I) according to the invention but especially to the hydroxamic acids (18). The phosphorus or arsenic ylid (10) may have a variety of substituents (*e.g.* trialkyl or unsymmetrical alkyl and/or aryl substituents) and is not intended to be limited to Ph_3P- or Ph_3As- as shown. When it is desired that R should denote hydroxy in compound (17), this may be achieved by hydrolysis of the corresponding ester compound (17) in which R is C_1-C_{10} alkoxy. If R denotes hydroxy in compound (17), the reaction of (17) to (18) may require activation of the acid group of compound (17).

Optionally (see Scheme 8) a substituted or unsubstituted 4-nitrophenylpropenal can be reacted with (10) to give the corresponding 4-nitrophenylhepta-2,4,6-trienoic

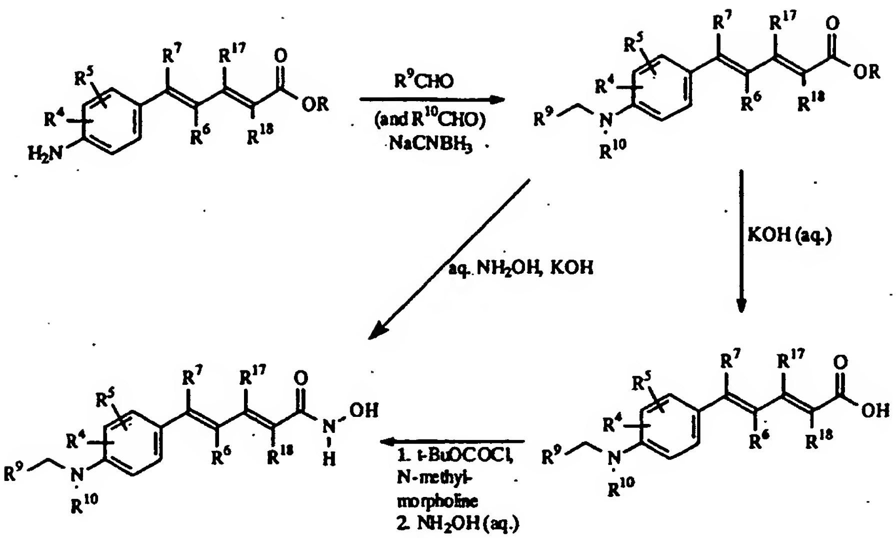
acid ester that is reduced to give the corresponding 4-amino compound that is then treated with an aromatic sulphonyl chloride or aromatic chloride to give the corresponding compound (17).

Scheme 9



In Scheme 9 is shown routes to carboxylic acids (22) and (25) and their ester derivatives, and also their hydroxamic acid derivatives (23) and (26). A Wittig or related process affords the carbonyl compounds (22). Here, a related process includes Horner-Wadsworth-Emmons or other modifications, and also use of the analogous arsenic ylides as well as use of compounds other than (21) (*e.g.* simple or complex enolates, or enolate equivalents of an appropriate carbonyl compound, such as enamino esters, enamino ketones or metal complexes derived from α-halo esters and related compounds). The carbonyl compound (22) so obtained can then be converted into other derivatives, but especially the hydroxamic acids (23). The phosphorus or arsenic ylid may have a variety of substituents (*e.g.* trialkyl or unsymmetrical alkyl and/or aryl substituents) and is not intended to be limited to Ph_3P- or Ph_3As- as shown. The carbonyl compounds (22) can also be reduced, typically with hydrogen and a catalysts (*e.g.* Pd, Ni, Co, *etc.*) or by hydrosilylation or hydride-acid systems and other processes to give the carboxylic acids (25) and their derivatives. In particular, the ester derivatives (22) and (25) can be converted, typically by aqueous hydroxylamine, but also by hydroxylamine derivatives with or without bases, respectively into the hydroxamic acids (23) and (26). The group R in reagent (21) and in compound (24) is hydroxy or C_1-C_{10} alkoxy. Preferably, R is C_1-C_{10} alkoxy and especially $-OCH_3$ or $-OCH_2CH_3$. When it is desired that R should denote hydroxy in compound (17), this may be achieved by hydrolysis of the corresponding ester compound (17) in which R is C_1-C_{10} alkoxy. When R=OH is desired in compound (22) or (25), this may be preferably achieved by standard methods of ester hydrolysis of the corresponding ester compound (22) or (25) formed in the preferred aspect when R is C_1-C_{10} alkoxy. If R is OH, the reaction of (22) to (23) and of (25) to (26) may require activation of the acid group.

Scheme 10



Scheme 10 shows how an intermediate (7) bearing an amino group can be converted into compounds of the invention where W is $-C(R^{11})(R^{12})-NR^{13}-$. In this particular scheme R^{11} and R^{12} are both hydrogen, although other reactants could readily be chosen in order to prepare compounds having other R^{11} and R^{12} groups. The reactant $R^{10}CHO$ is shown in parentheses because it need not be used if it is desired that R^{10} be hydrogen.

A preferred example obtained using procedures in Scheme 10 include the reaction of an amine (7) with a benzaldehyde in the presence of formaldehyde and sodium cyanoborohydride to give the corresponding tertiary amine whose ester group is subsequently converted into the corresponding hydroxamic acid.

In the Schemes, hydroxylamine is shown as the means of obtaining a hydroxamic acid. While this is the preferred reagent, especially in the form of an aqueous 50% solution, and in its action upon methyl or ethyl esters that are to undergo hydroxamation, this protocol is not intended to exclude other variants. For example, the use of a hydroxylamine salt, especially hydroxylamine hydrochloride (or hydrates thereof) in combination with a base or alkali, especially sodium hydroxide or potassium hydroxide, and commonly followed by filtration to give a "salt-free" solution of hydrazine (often in an alcoholic solvent) is an effective procedure. Also effective is the activation of carboxylic acids (*e.g.* by chloroformates such as *iso*-butyl chloroformate or ethyl chloroformate) and subsequent treatment with hydroxylamine or its equivalent in

the form of derivatives with or without additional reagents such as a base. Thus, any known method of hydroxamation may be considered.

The compounds of the invention are inhibitors of histone deacetylase (HDAC). They may therefore be used to treat a HDAC-mediated disorder. A therapeutically effective amount of a compound of the invention is administered to a subject, typically a human being, having such a disorder. The condition of the subject can thus be improved. Symptoms associated with the disorder may be ameliorated.

Compounds of the invention may also be inhibitors of DNA methyl transferase. They may therefore be used to treat diseases and disorders for which inhibition of methyl transferase is relevant. The compounds may target a variety of cancers, including prostate, colon and esophageal cancers.

HDAC-mediated disorders that may be treated according to the invention include cancer such as breast cancer, colon cancer, colorectal cancer, esophageal cancer, glioma, leukemia, lung small and non-small cell cancers, neuroblastoma, prostate cancer, thoracic cancer, melanoma, ovarian cancer, cervical cancer and renal cancer; cardiac hypertrophy; hematological disorders such as haemoglobinopathies, thalessemia and sickle cell anemia; and genetic-related metabolic disorders such as cystic fibrosis, peroxisome biogenesis disorders and adrenoleukodystrophy. HDAC inhibitors have also been proposed for stimulating hematopoietic cells *ex vivo*, ameliorating protozoal parasitic infection, accelerating wound healing and protecting hair follicles.

A compound of the invention may be used in combination with another chemotherapeutic or antineoplastic agent in the treatment of a cancer. Examples of such other chemotherapeutic or antineoplastic agents include mitoxantrone; Vinca alkaloids such as vincristine and vinblastine; anthracycline antibiotics such as daunorubicin and doxorubicin; alkylating agents such as chlorambucil and melphalan; taxanes such as paclitaxel; antifolates such as methotrexate and tomudex; epipodophyllotoxins such as etoposide; camptothecins such as irinotecan and its active metabolite SN-38 and DNA methylation inhibitors such as the DNA methylation inhibitors disclosed in WO 02/085400.

According to the invention, therefore, products are provided which contain a compound of the invention and another chemotherapeutic or antineoplastic agent as a combined preparation for simultaneous, separate or sequential use in creating a cancer.

The compound of the invention and the other agent may be administered together or, if separately, in any order as determined by a physician.

The present compounds can be administered in a variety of dosage forms, for example orally such as in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The present compounds may therefore be given by injection or infusion.

The dosage depends on a variety of factors including the age, weight and condition of the patient and the route of administration. The dosage for a particular patient will be determined by a physician. Typically, however, the dosage adopted for each route of administration when a compound of the invention is administered to adult humans is 0.001 to 500 mg/kg, most commonly in the range of 0.01 to 100 mg/kg, body weight, for instance 0.01 to 50 mg/kg. Such a dosage may be given, for example, from 1 to 5 times daily by bolus infusion, infusion over several hours and/or repeated administration. The dosage and timing of administration of, for example, another chemotherapeutic or antineoplastic agent which may be given to a cancer patient with a compound of the invention will similarly be dependent on a variety of factors and will be determined by a physician.

A compound of any of the formulae (I) to (VII) described above or a pharmaceutically acceptable salt thereof is formulated for use as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier or diluent. The compositions are typically prepared following conventional methods and are administered in a pharmaceutically suitable form. Preferred pharmaceutical compositions are sterile and pyrogen-free. Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer.

Compositions suitable for oral administration may, if required, contain a colouring or flavouring agent. Typically, a capsule or tablet comprises from 5 to 500 mg, preferably 10 to 500 mg, more preferably 15 to 100 mg, of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Solid oral forms of the pharmaceutical compositions of the invention may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid,

magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The following Examples illustrate the invention. Several Preparation Examples are also provided. Starting materials were purchased from Avocado or Aldrich and used as supplied, unless otherwise stated. The following compounds were prepared by literature methods:

- (triphenyl-γ^5-phosphanylidene)acetic acid ethyl ester **(5b)** (J. J. Cappon, J. Boart, G. A. M. Walle, J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, **1991**, *5*, 158);
- (1-ethoxycarbonylethyl)triphenylphosphonium bromide (I. Shimizu, K. Hayashi, N. Ide and M. Oshima, *Tetrahedron*, **1991**, *47*, 2991);
- *(E)*-4-(triphenyl-γ^4-arsanylidene)but-2-enoic acid ethyl ester bromide (Y. Huang, Y. Shen, J. Zhang and S. Zhang, *Synthesis*, **1985**, 57);
- *(E)*-2-methyl-3-(4-nitrophenyl)propenal **(4b)** (H. Hirata, H. Nakata, K. Yamada, K. Okuhara and T. Naito, *Tetrahedron*, **1961**, *14*, 252);

- *(E)*-2-methyl-3-(4-dimethylaminophenyl)propenal (**4i**) (V. Sunjic, M. Majeric and Z. Hamersak, *Croat. Chem. Acta*, **1996**, *69*, 643);
- *(2E,4E)*-2,4-dimethyl-5-(*p*-nitrophenyl)penta-2,4-dienal (**14a**) (E. Suzuki and S. Inoue, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 404);
- (ethoxycarbonylmethylene)triphenylphosphorane (R. W. Lang and H.-J. Hansen, *Org. Synth.*, **1994**, *62*, 203);
- 2-(4-nitrophenyl)-1,3-dioxane (S. Fukuzawa, T. Tsuchimoto and T. Hiyama, *J. Org. Chem.*, **1997**, *62*, 151);
- 4-(1,3-dioxan-2-yl)phenylamine (M. C. Cesa, J. E. Rinz and T. T. Kopp, *U. S. Pat.*, **1998**, 4,868,061; and
- [(2*E*,4*E*)-6-methoxy-6-oxo-2,4-hexadienyl]triphenylphosphonium bromide (E. Vedejs and J. P. Bershas, *Tetrahedron Lett.*, **1975**, *16*, 1359).

<u>Preparation Example 1: 4-chloro-*N*-(4-formylphenyl)benzamide (2g)</u>

2-(4-aminophenyl)-[1,3] dioxane (1.37 g, 7.62 mmol) was dissolved in pyridine (15 mL) and 4-chlorobenzoyl chloride (1.74 g, 9.94 mmol) was then added dropwise to the stirred solution over 10 min and the mixture subsequently stirred for at 20 °C 5 h. The mixture was then added to dichloromethane (100 mL) and water (100 mL), and the whole gently shaken. The organic layer was separated and washed with 2 M hydrochloric acid (4 x 50 mL), then the organic layer was poured into a mixture of methanol (100 mL) and water (100 mL). More methanol was added until the solution became homogenous. A catalytic amount of *p*-toluenesulphonic acid was then added to the stirred solution followed by dropwise addition of 10 M hydrochloric acid (15 mL). The mixture was subsequently stirred at 20 °C 24 h. The solvents were evaporated and the residue suspended in water (100 mL) prior to extraction with dichloromethane (3 x 50 mL). The organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate (3 x 50 mL), and then with water (50 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to give the title compound (0.97 g, 49%) as a fine pale yellow powder, mp 183-185 °C.

<u>Preparation Example 2: *N*-(4-formylphenyl)-4-methoxybenzamide (2h)</u>

2-(4-aminophenyl)-[1,3] dioxane (1.00 g, 5.58 mmol) was dissolved in pyridine (11 mL) and 4-methoxybenzoyl chloride (1.05 g, 6.10 mmol) was then added dropwise

to the stirred solution over 10 min and the mixture subsequently heated at reflux for 14 h. The solvent was evaporated and the residue dissolved in dichloromethane (50 mL) to give a solution that was washed with 2 M hydrochloric acid (3 x 40 mL). The organic layer was then separated and poured into water (100 mL). Methanol was then added until the solution became homogenous. A catalytic amount of *p*-toluenesulfonic acid was then added to the stirred solution and the mixture was subsequently stirred at 25 °C 24 h. The solvents were evaporated and the residue suspended in water (100 mL) prior to extraction with dichloromethane (3 x 50 mL). The organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate (3 x 50 mL), and then with water (50 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to give the title compound (0.45 g, 32%) as a fine pale yellow powder, mp 142-144 °C.

Preparation Example 3: (2*E*,4*E*)-4-methyl-5-(4-nitrophenyl)penta-2,4-dienoic acid ethyl ester (6c)

To a stirred solution of (*E*)-2-methyl-3-(4-nitrophenyl)propenal (1.00 g, 5.24 mmol) in toluene (6.0 mL) was added (triphenyl-γ^5-phosphanylidene)acetic acid ethyl ester (**5b**) (2.76 g, 7.93 mmol) at 25 °C. The mixture was heated to 40 °C and stirring was continued at 40 °C for 4 h. The mixture was then evaporated and the residue purified by flash chromatography on silica gel (1:9 ethyl acetate: 60-80 °C petroleum ether) to give the title compound (1.26 g, 92%) as crystalline yellow platelets, mp 124-125 °C. IR (nujol) ν_{max} 1712 (COOEt), 1625 (C=C), 1519 (NO_2) cm-^{1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.09 (2H, d, *J*=8Hz, ArH), 7.35 (3H, dd, *J*=8 and 13 Hz, ArH and CH=CH-CHO), 6.73 (1H, s, Ph-CH), 5.99 (1H, d, *J*=13 Hz, CH-CHO), 4.12 (2H, q, *J*=7Hz, CH_2O), 1.94 (3H, s, $=CCH_3$), 1.18 (3H, t, *J*=7Hz, CH_3).

Preparation Example 4: (2*E*,4*E*)-2,4-dimethyl-5-(4-nitrophenyl)penta-2,4-dienoic acid ethyl ester (6e)

To a cooled suspension of (1-ethoxycarbonylethyl)triphenylphosphonium bromide (1.0 g, 2.25 mmol) in dry THF (10 mL) was added dropwise *n*-butyllithium (1.6 M in hexanes, 1.4 mL, 2.3 mmol) at 0 °C. Stirring was continued at 0 °C for 20 min, then 10 min at 20 °C. To the above solution was added (*E*)-2-methyl-3-(4-nitrophenyl)propenal (**4b**) (0.36 g, 1.88 mmol) in portions over 5 min. The mixture was then stirred at 20 °C for 16 h. The mixture was then evaporated

and the residue purified by flash chromatography on silica gel (1:4 ethyl acetate: 60-80 °C petroleum ether) to give a residue that was recrystallised from methanol to give the title compound (0.38 g, 73%) as yellow platelets, mp 80-81 °C; IR (nujol) ν_{max} 1697 (COOEt), 1606 and 1589 (C=C), 1508 (NO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.16 (2H, d, *J*=9.0 Hz, ArH), 7.37 (2H, d, *J*=9.0 Hz, ArH), 7.19 (1H, s, C*H*=CH-COO), 6.54 (1H, s, Ph-C*H*), 4.14 (2H, q, *J*=7 Hz, CH_2O), 2.03 (6H, s, $=CCH_3$), 1.29 (3H, t, *J*=7 Hz, CH_3CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.91 (COO), 144.13, 142.29, 138,48, 131.75, 130.16, 129.18, 123.97 (ArC=C and C=C), 61.34 (CH_2O), 18.97, 14.74, 14.68 (CH_3). Elemental analysis: $C_{15}H_{17}NO_4$. Calc. (%) C: 65.45, H: 6.18, N: 5.09. Found (%) C: 64.93, H: 6.15, 4.88.

<u>Preparation Example 5: (2*E*,4*E*)-5-(4-Nitrophenyl)penta-2,4-dienoic acid ethyl ester (6a)</u>

To a suspension of 3-ethoxycarbonylallylidenetriphenylarsonium bromide (1.40 g, 2.81 mmol) in dry THF (12 mL) was added dropwise *n*-butyllithium (2.5 M in hexanes, 1.1 mL, 2.81 mmol) at 0 °C. Stirring was continued at 0 °C for 20 min, then 10 min at 20 °C. To the above solution was added *p*-nitrobenzaldehyde (0.385 g, 2.55 mmol) in portions over 5 min. The mixture was then stirred at 20 °C for 16 h. The mixture was evaporated and the residue purified by flash chromatography on silica gel (1:4 ethyl acetate: 60-80 °C petroleum ether) to give a residue that was recrystallised from methanol to give the title compound (0.51 g, 81%) as yellow prisms, mp 114-115 °C. IR (nujol) ν_{max} 1710 (COO), 1625 (C=C), 1512 (ArC=C) cm^{-1}; δ_H ^1H NMR (300 MHz, $CDCl_3$) δ_C 8.03 (2H, d, *J*=9 Hz, ArH), 7.40 (2H, d, *J*=9 Hz, ArH), 7.26 (1H, dd, *J*= 10 and 15 Hz, C*H*=CH-COO), 6.86-6.78 (2H, m, Ph-C*H*=C*H*), 5.82 (1H, d, *J*=15 Hz, CH-COO), 4.02 (2H, q, *J*=7 Hz, CH_2O), 1.11 (3H, t, *J*=7 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.84 (COO), 143.39, 142.68, 137.52, 130.81, 127.96, 127.96, 124.63, 124.53 (ArC=C and CH=CH), 60.98 (CH_2O), 14.64 (CH_3). Elemental analysis: $C_{13}H_{13}NO_4$. Calc. (%): C: 63.15, H: 5.26, N: 5.66. Found (%): C: 63.11, H: 5.33, N: 5.64.

<u>Preparation Example 6: (2*E*,4*E*)-5-(4-aminophenyl)penta-2,4-dienoic acid ethyl ester (7a)</u>

To a stirred solution of iron(II) sulfate heptahydrate (6.88 g, 24.7 mmol) in water (26 mL) and 0.880 concentrated aqueous ammonia (13 mL) at 60 °C was added a solution of (2*E*,4*E*)-5-(4-nitrophenyl)penta-2,4-dienoic acid ethyl ester (Preparation Example 5, **6a**) (0.51 g, 2.06 mmol) in ethanol (20 mL). The mixture was then heated to 60 °C for 10 min. The solution was allowed to cool, extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was recrystallised from methanol - diethyl ether - 60-80 °C petroleum ether to give the title compound (0.37 g, 83%) as orange needles, mp=91-92 °C. IR (nujol) ν_{max} 3398 and 3332 (NH_2), 1697 (COO), 1622 (C=C), 1512 (ArC=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.25 (1H, dd, *J*=10 and 15 Hz, C*H*=CH-COO), 7.09 (2H, d, *J*=8 Hz, ArH), 6.60 (1H, d, *J*=15 Hz, CH-COO), 6.55-6.44 (3H, m, ArH and Ph-CH=CH), 5.71 (1H, d, *J*=15 Hz, Ph-CH), 4.03 (2H, q, *J*=7 Hz, CH_2O), 3.62 (2H, br s, NH_2), 1.13 (3H, t, *J*=7Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.79 (COO), 147.93, 145.84, 141.21, 129.75, 127.01, 123.00, 119.42, 115.42 (ArC=C and CH=CH), 60.50 (CH_2O), 14.74 (CH_3). Elemental analysis: $C_{13}H_{15}NO_2$. Calc. (%): C: 71.88, H: 6.91, N: 6.45. Found (%): C: 71.97, H: 6.90, N: 6.36.

Preparation Example 7: (2*E*,4*E*)-5-(4-aminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (7b)

To a stirred solution of iron(II) sulfate heptahydrate (9.71 g, 34.9 mmol) in water (40 mL) and 0.880 concentrated aqueous ammonia (18 mL) at 40 °C was added a solution of (2*E*,4*E*)-4-methyl-5-(4-nitrophenyl)penta-2,4-dienoic acid ethyl ester (Preparation Example 3; **6c**) (0.760 g, 2.91 mmol) in ethanol (25 mL). The mixture was then heated to 60 °C for 10 min. The solution was allowed to cool, extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give the title compound (0.62 g, 92%) as yellow prisms, mp 107-108 °C. IR (film) ν_{max} 1720 (COOEt), 1530 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.38 (1H, d, *J*=15Hz, C*H*=CH-CHO), 7.11 (2H, d, *J*=8Hz, ArH), 6.62 (1H, s, Ph-C*H*), 6.60 (2H, d, *J*= 8Hz, ArH), 5.80 (1H, d, *J*=15Hz, C*H*-CHO), 4.09 (2H, q, *J*=7 Hz, CH_2O), 3.73 (2H, br s, NH_2), 1.94 (3H, s, =CCH_3), 1.24 (3H, t, *J*=7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.04 (C=O), 151.16, 147.03, 143.57, 137.79, 136.19, 131.58, 123.91, 115.02 (ArC=C and C=C), 60.51 (CH_2O), 14.66, 14.18 (CH_3).

Elemental analysis: $C_{14}H_{17}NO_2$. Calc (%) C: 72.70, H: 7.40, N: 6.05. Found (%) C: 72.65, H: 7.45, N: 6.00.

Preparation Example 8: (2*E*,4*E*)-5-(4-aminophenyl)-2,4-dimethylpenta-2,4-dienoic acid ethyl ester (7c)

To a stirred solution of iron(II) sulfate heptahydrate (3.0 g, 10.8 mmol) in water (10 mL) and 0.880 concentrated aqueous ammonia (6 mL) at 60 °C was added a solution of (2*E*,4*E*)-5-(4-nitrophenyl)-2,4-dimethylpenta-2,4-dienoic acid ethyl ester (Preparation Example 4; **6e**) (0.25 g, 0.09 mmol) in ethanol (10 mL). The mixture was then heated to 60 °C for 15 min. The solution was allowed to cool, extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The mixture was then evaporated and the residue purified by flash chromatography on silica gel (1:4 ethyl acetate: 60-80 °C petroleum ether) to give the title compound as an oil.

Example 1: (2E,4E)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (8a)

To a stirred solution of (2*E*,4*E*)-5-(4-aminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Preparation Example 7; **7b**) (0.35 g, 1.52 mmol) in pyridine (8.0 mL) at 25 °C was added benzenesulfonyl chloride (0.39 mL, 3.04 mmol) by means of a stainless steel cannula. The stirred mixture was then heated and maintained at 90 °C for 2 h. Crushed ice (2.5 g) was added cautiously and the resulting suspension was filtered through a sintered glass funnel. The solid was dried in air and recrystallised from ethanol to give the title compound (0.41 g, 73%) as dark yellow platelets, mp 134-136 °C.

Example 2: (2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)penta-2,4-dienoic acid ethyl ester (8b)

A solution of (2*E*,4*E*)-5-(4-aminophenyl)penta-2,4-dienoic acid ethyl ester (Preparation Example 6, 7a) (0.32 g, 1.47 mmol) and *p*-chlorobenzenesulfonyl chloride (0.405 g, 1.91 mmol) in pyridine (3 mL) was heated at reflux for 6 h, then removed to ambient temperature and stirred for 12 h. Evaporation gave a residue that was dissolved in dichloromethane (30 mL) and the solution washed with 1.2 M hydrochloric acid (20

mL) then with saturated aqueous sodium chloride (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was recrystallised from methanol to give the title compound (0.42 g, 73%) as orange prisms, mp 191-192 °C. IR (nujol) ν_{max} 3238 (NH), 1683 (C=O), 1625 (C=C), 1512 (ArC=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.92 (2H. d, *J*=8 Hz, ArH), 7.41-7.28 (5H, m, ArH and C*H*=CH-C=O), 6.99 (2H, d, *J*=9 Hz, ArH), 6.70 (2H, m, Ph-CH and Ph-CH=C*H*), 5.91 (1H, d, *J*=15 Hz, CH-C=O), 4.15 (2H, q, *J*=7 Hz, CH_2O), 1.21 (3H, t, *J*=7 Hz, CH_3); ^{13}CNMR (75 MHz, $CDCl_3$) δ_C 166.04 (C=O), 143.24, 138.80, 137.93, 136.50, 135.60, 132.51, 128.45, 127.64, 127.27, 125.35, 120.57 (ArC=C and C=C), 59.41 (CH_2O), 13.29 (CH_3). Elemental analysis: $C_{19}H_{18}ClNO_4S$. Calc. (%) C: 58.23, H: 4.59, N: 3.57. Found (%) C: 57.85, H: 4.64, N: 3.49.

<u>Example 3: (2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)penta-2,4-dienoic acid ethyl ester (8c)</u>

A solution of (2*E*,4*E*)-5-(4-aminophenyl)penta-2,4-dienoic acid ethyl ester (Preparation Example 6, 7a) (0.35 g, 1.61 mmol) and *p*-methoxybenzenesulfonyl chloride (0.50 g, 2.41 mmol) in pyridine (3 mL) was heated at reflux for 24 h. The pyridine was removed under reduced pressure and the residue was dissolved in dichloromethane (30 mL). The solution was washed with 1.2 M hydrochloric acid (20 mL) then with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was recrystallised from methanol to give the title compound (0.56 g, 90%) as the hemi-hydrate, a pale yellow solid, mp 181-182 °C. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J*=8 Hz, ArH), 7.32 (1H, dd, *J*= 15 and 10 Hz, C*H*=CH-C=O), 7.28 (2H. d, *J*=8 Hz, ArH), 7.01 (2H, d, *J*=9Hz, ArH), 6.81 (2H, d, *J*=8 Hz, ArH), 6.70 (2H, m, Ph-CH and Ph-CH=C*H*), 5.87 (1H, d, *J*=15 Hz, CH-C=O), 4.06 (2H, q, *J*=7 Hz, CH_2O), 3.76 (3H, s, CH_3O), 1.20 (3H, t, *J*=7 Hz, CH_3); ^{13}CNMR (75 MHz, $CDCl_3$) δ_C 167.53 (C=O), 144.84, 139.67, 137.76, 133.16, 130.85, 129.83, 128.59, 126.27, 121.61, 121.34, 114.69, 113.43 (ArC=C and C=C), 60.80 (CH_2O), 55.98 (CH_3O), 14.70 (CH_3). Elemental analysis: $C_{20}H_{21}NO_5S$, $1/2H_2O$. Calc. (%) C: 60.60, H: 5.55, N: 3.53. Found (%) C: 60.94, H: 5.51, N: 3.57.

<u>Example 4: (2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (8d)</u>

A stirred solution of (2*E*,4*E*)-5-(4-aminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Preparation Example 7; 7b) (0.30 g, 1.29 mmol) and *p*-chlorobenzenesulfonyl chloride (0.548 g, 2.58 mmol) in pyridine (8 mL) was heated at reflux for 2 h. Dichloromethane (20 mL) was then added to the solution which was then washed with 1.2 M hydrochloric acid (3 x 10 mL) then with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica gel (1:4 ethyl acetate: 60-80 °C petroleum ether) to give a solid which was recrystallised from methanol to give the title compound (0.23 g, 44%) as yellow needles, mp 156-157 °C. IR (nujol) ν_{max} 3180 (NH), 1683 (COO), 1625 (C=C), 1508 (ArC=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.85 (2H, d, *J*=9 Hz, ArH), 7.58 (1H, d, *J*=15 Hz, C*H*=CH-CHO), 7.53 (1H, s, NH), 7.52 (2H, d, *J*= 8 Hz, ArH), 7.36 (2H, d, *J*=9 Hz, ArH), 7.28 (2H, d, *J*= 8 Hz, ArH), 6.83 (1H, s, Ph-C*H*), 6.07 (1H, d, *J*=15 Hz, C*H*-CHO), 4.35 (2H, q, *J*=7Hz, CH_2O), 2.10 (3H, s, $=CCH_3$), 1.44 (3H, t, J=7 Hz, CH_3CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.77 (COO), 149.90, 140.12, 138.00, 137.91, 135.92, 134.65, 134.48, 131.02, 129.81, 129.05, 121.57, 118.15 (ArC=C and C=C), 60.79 (CH_2O), 14.69, 14.11 (CH_3). Elemental analysis: $C_{20}H_{20}NClO_4S$. Required (%) C: 59.18, H: 4.93, N: 3.45. Found (%): C: 58.73, H: 4.63 , N: 3.27 .

<u>**Example 5: (2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid (8e)**</u>

A stirred solution of (2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl-4-methylpenta-2,4-dienoic acid ethyl ester (Example 4; 8d) (0.30 g, 0.73 mmol) and lithium hydroxide (0.154 g, 3.65 mmol) in THF (10 mL) and water (10 mL) was heated at 70 °C for 16 h. The mixture was extracted with diethyl ether (10 mL), acidified to pH 2 with 1.2 M hydrochloric acid and then extracted with ethyl acetate (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was recrystallised from ethyl acetate to give the title compound (0.25 g, 91%) as a yellow solid, mp 218-220 °C. mp=218-220 °C; IR (nujol) ν_{max} ^1H NMR (300 MHz, DMSO-d_6); δ_H 7.97 (2H, d, *J*=8 Hz, ArH), 7.81 (2H, d, *J*=8 Hz, ArH), 7.55-7.48 (M, 3H, ArH and C*H*=CH-C=O), 7.32 (2H, d, *J*=8 Hz, ArH), 6.76 (1H, s, Ph-CH), 6.08 (1H, d, *J*=15 Hz, CH-C=O), 2.14 (3H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 168.04 (C=O), 149.50, 138.75, 138.25, 137.84, 137.27, 133.61, 132.67, 130.89, 129.84, 128.93, 120.09, 118.44

(ArC=C and C=C), 13.92 (CH_3). Elemental analysis: $C_{18}H_{16}NClO_4S$. Calc. (%) C: 57.21, H: 4.23, N: 3.70. Found (%) C: 56.78, H: 4.53, N: 3.58.

Example 6: (2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (8f)

A stirred solution of (2*E*,4*E*)-5-(4-aminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Preparation Example 7; 7b) (0.30 g, 1.29 mmol) and *p*-methoxybenzenesulfonyl chloride (0.535 g, 2.58 mmol) in pyridine (8 mL) was heated at reflux for 2 h. Dichloromethane (20 mL) was then added and the solution washed with 1.2 M hydrochloric acid (3 x 10 mL) then with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica gel (3:7 ethyl acetate: 60-80 °C petroleum ether) to give a solid which was recrystallised from methanol to give the title compound (0.43 g, 83%) as yellow prisms, mp 131-132 °C. mp=131-132 °C, IR (nujol) ν_{max} 3199 (NH), 1683 (COO), 1625 (C=C), 1508 (ArC=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.98 (2H, d, *J*=9 Hz, ArH), 7.58 (1H, d, *J*=15.5 Hz, C*H*=CH-CHO), 7.51 (1H, s, NH), 7.45 (2H, d, *J*= 8 Hz, ArH), 7.34 (2H, d, *J*=9 Hz, ArH), 7.14 (2H, d, *J*= 8 Hz, ArH), 6.94 (1H, s, Ph-C*H*), 6.22 (1H, d, *J*=16 Hz, C*H*-CHO), 4.40 (2H, q, *J*=7Hz, CH_2O), 4.03 (3H, s, CH_3O), 2.21 (3H, s, =CCH_3), 1.56 (3H, t, J=7 Hz, CH_3CH_2O); ^{13}CNMR (75 MHz, $CDCl_3$) δ_C 167.77 (COO), 163.29, 150.02, 138.19, 136.65, 134.31, 133.82, 131.10, 130.91, 129.82, 121.06, 117.91, 114.67 (ArC=C and C=C), 60.74 (CH_3O), 55.95 (CH_2O), 14.70, 14.10 (CH_3). Elemental analysis: $C_{21}H_{23}NO_5S$, 1/8H_2O. Required (%) C: 62.84, H: 5.73, N: 3.49. Found (%): C: 62.49, H: 5.76, N: 3.47.

Example 7: (2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-2,4-dimethylpenta-2,4-dienoic acid ethyl ester (8g)

A stirred solution of (2*E*,4*E*)-5-(4-aminophenyl)-2,4-dimethylpenta-2,4-dienoic acid ethyl ester (Preparation Example 8; 7c) (0.15 g, 0.61 mmol) and *p*-methoxybenzenesulfonyl chloride (0.253 g, 1.22 mmol) in pyridine (5 mL) was heated at 90 °C for 4 h. The pyridine was removed under reduced pressure and the residue dissolved in dichloromethane (20 mL). The solution was washed with 1.2 M hydrochloric acid (2 x 10 mL) then with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on

silica gel (3:7 ethyl acetate: 60-80 °C petroleum ether) to give the title compound (0.23 g, 91%) as an oil, a mixture of diastereoisomers.

Example 8: (2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid (8h)

To a stirred solution of (2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Example 1, 8a) (0.40 g, 1.08 mmol) in THF (5.0 mL) and water (5.0 mL) was added lithium hydroxide (0.15 g, 6.25 mmol). The stirred mixture was then heated and maintained at 80 °C for 5 h. The mixture was allowed to cool, transferred to a separating funnel and extracted with diethyl ether (3 x 10 mL). The aqueous layer was then acidified to pH 2 with 1M hydrochloric acid (approx. 2.5 mL), extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered through a fluted filter paper and evaporated to give the title compound (0.31 g, 84%) as bright orange platelets, mp 162-163 °C.

Example 9: (2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid (8i)

A stirred suspension of (2E,4E)-5-(4-(4-methoxybenzenesulfonylamino)phenyl-4-methylpenta-2,4-dienoic acid ethyl ester (Example 6; 8f) (0.15 g, 0.37 mmol) and lithium hydroxide (0.045 g, 1.88 mmol) in THF (2 mL) and water (2 mL) was heated at 70 °C for 3.5 h. The mixture was extracted with diethyl ether (20 mL), acidified to pH 2 with 1.2 M hydrochloric acid and then extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried (MgSO4), filtered and evaporated to give the title compound (0.10 g, 73%) as a white solid, mp 215 °C.

Example 10: (2*E*,4*E*)-5-(4-(4-chlorobenzoylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (8k)

p-Chlorobenzoyl chloride was prepared by a modification of a procedure described in: J. P. Dickie, M. E. Loomans, T. M. Farley and F. M. Strong, *J. Med. Chem.*, **1968**, *6*, 424. *p*-Chlorobenzoic acid (0.78 g, 4.98 mmol) was dissolved in toluene (20 mL) and one drop of DMF added. This mixture was cooled at –30 °C, and oxalyl chloride (0.43 mL, 5.01 mmol) added dropwise over 10 min. The mixture was allowed to warm to 20 °C, the solvent evaporated and the residue redissolved in dry

toluene (10 mL) to give a solution of *p*-chlorobenzoyl chloride.

(2*E*,4*E*)-5-(4-Aminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Preparation Example 7; **7b**) (1.00 g, 4.32 mmol) was dissolved in dry toluene (26 mL) and triethylamine (0.42 mL, 3.03 mmol). 1,2-Phenylene phosphorochloridite (0.56 g, 3.21 mmol) in dry toluene (15 mL) was then added to the mixture, and the reaction heated at reflux for 2.5 h. A solution of *p*-chlorobenzoyl chloride was then added, and the mixture heated at reflux for a further 24 h. The solvent was evaporated and the residue dissolved in dichloromethane (50 mL). The solution was washed with 2 M hydrochloric acid (3 x 40 mL), then water (2 x 40 mL) and lastly saturated aqueous sodium hydrogen carbonate (3 x 40 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was recrystallised from propan-2-ol to give the title compound (0.73 g, 45%) as white plates, mp 169-170 °C.

Example 11: (2*E*,4*E*)-5-(4-(4-methoxybenzoylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (8l)

(2*E*,4*E*)-5-(4-Aminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Preparation Example 7; **7b**) (1.00 g, 4.33 mmol) was dissolved in dry toluene (13 mL) and triethylamine (1.26 mL, 8.96 mmol). *o*-Phenylene phosphorochloridite (0.98 g, 5.62 mmol) in dry toluene (6.2 mL) was then added to the mixture, and the reaction heated at reflux for 2.5 h. *p*-Chlorobenzoic acid (0.37 g, 2.37 mmol) was then added, and the mixture heated at reflux for a further 24 h. The solvent was evaporated and the residue purified by flash chromatography on silica gel (80 g) (1:4 ethyl acetate: 60-80 °C petroleum ether) to give a residue was recrystallised from propan-2-ol to give the title compound (0.07 g, 5%) as yellow platelets, mp 121-122 °C.

Example 12: (2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid hydroxyamide (9a)

To a stirred solution of hydroxylamine hydrochloride (0.56 g, 8.06 mmol) in methanol (4.0 mL) at 40 °C was added a solution of potassium hydroxide (0.45 g, 8.04 mmol) in methanol (4.0 mL). The solution was cooled to 0 °C and the suspension filtered through a glass funnel. To the stirred filtrate was added (2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Example 1, **8a**) (0.30 g, 0.81 mmol) at 25 °C. To the stirred mixture at 25 °C was

added potassium hydroxide (0.20 g, 3.57 mmol) in portions over 30 min. The mixture was then stirred at 25 °C for a further 4 h. Water (4.0 mL) was added and the mixture was acidified to pH 6 with 0.5 M hydrochloric acid, and extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered through a fluted filter paper and evaporated to give a solid which was recrystallised from benzene to give the title compound (0.20 g, 69%) as bright orange crystals, mp 137-139 °C.

Example 13: (2*E*,4*E*)-5-(4-chlorobenzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid hydroxyamide (9b)

To a suspension of (2*E*,4*E*)-5-(4-4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Example 4; 8d) (0.45 g, 1.1 mmol) in THF (6 mL) cooled to 0 °C was added dropwise a 50% aqueous solution of hydroxylamine (0.66 g, 20.0 mmol) and potassium hydroxide (0.197 g, 3.52 mmol) in methanol (2.0 mL) at 0 °C over 30 min. Stirring was continued for a further 30 min at 0 °C, then at 20 °C for 4 days. Water (5.0 mL) was then added and the mixture was acidified to pH 6 with 1.2 M hydrochloric acid, and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a solid which was recrystallised from ethyl acetate to give the title compound (0.24 g, 44%) as a white powder, mp 177-178 °C (decomp.); IR (nujol) ν_{max} 3436 (OH), 3217 (NH), 1664 (C=O), 1631 (C=C), 1502 (ArC=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 8.92 (1H, br s, NH), 7.79 (2H, d, *J*=9 Hz, ArH), 7.61 (2H, d, *J*=9 Hz, ArH), 7.36 (1H, s, $NHSO_2$), 7.29-7.21 (3H, m, ArH, C*H*=CH-COO), 7.13 (2H, d, *J*=9 Hz, ArH), 6.75 (1H, s, Ph-C*H*), 5.90 (1H, d, *J*=15 Hz, CH-COO), 1.94 (3H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 163.46 (C=O), 143.97, 138.75, 138.24, 136.92, 135.97, 133.71, 133.02, 130.71, 129.84, 128.94, 120.17, 118.47 (ArC=C and C=C), 14.06 (CH_3). Elemental analysis: $C_{18}H_{17}N_2ClO_4S$. Calc (%) C: 55.03, H: 4.33, N: 7.13. Found (%) C: 54.85, H: 4.61, N: 6.89.

Example 14: (2*E*,4*E*)-5-(4-methoxybenzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid hydroxyamide (9c)

To a suspension of (2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester (Example 8, 8f) (0.70 g, 1.74 mmol) in THF (10 mL) cooled to 0 °C was added dropwise a 50% aqueous solution of hydroxylamine

(0.52 g, 0.78 mmol) and potassium hydroxide (0.31 g, 5.54 mmol) in methanol (3.0 mL) at 0 °C over 30 min. Stirring was continued for a further 30 min at 0 °C, then at 20 °C for 48 h. Water (10 mL) was then added and the mixture was acidified to pH 6 with 1.2 M hydrochloric acid, and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a solid which was recrystallised from ethyl acetate to give the title compound (0.40 g, 59%) as a yellow powder, mp 171-172 °C (decomp.); IR (nujol) ν_{max} 3456 (OH), 3359 (NH), 1664 (C=O), 1649 (C=C), 1508 (ArC=C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_H 8.89 (1H, br s, NH), 7.69 (2H, d, J=9 Hz, ArH), 7.10 (1H, d, J=15 Hz, C*H*=CH-C=O), 7.05 (4H, m, ArH), 6.72 (1H, s, Ph-C*H*), 5.99 (1H, d, J=15 Hz, CH-C=O), 3.76 (3H, s, CH_3O), 1.92 (3H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 162.85 (C=O), 144.01, 137.56, 136.09, 133.45, 132.46, 131.58, 130.62, 129.23, 119.61, 118.31, 114.78 (ArC=C and C=C), 55.99 (CH_3O), 14.06 (CH_3). Elemental analysis: $C_{19}H_{20}N_2O_5S$, 1/4H_2O. Calc (%) C: 58.1, H: 5.22, N: 7.13. Found (%) C: 58.33, H: 5.30, N: 6.89.

Example 15: (2*E*,4*E*)-5-(4-methoxybenzenesulfonylaminophenyl)penta-2,4-dienoic acid hydroxyamide (9d)

To a suspension of (2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl) penta-2,4-dienoic acid ethyl ester (Example 3, **8c**) (0.47 g, 1.21 mmol) in THF (10 mL) cooled to 0 °C was added dropwise a 50% aqueous solution of hydroxylamine (0.72 g, 10.9 mmol) and potassium hydroxide (0.23 g, 4.11 mmol) in methanol (5.0 mL) at 0 °C over 30 min. Stirring was continued for a further 30 min at 0 °C, then at 20 °C for 48 h. Water (10 mL) was then added and the mixture was acidified to pH 6 with 1.2 M hydrochloric acid, and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a solid which was recrystallised from ethyl acetate to give the title compound (0.28 g, 62%) as a pale yellow powder, mp 181-182 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6) δ_H 7.90 (2H, d, J=9 Hz, ArH), 7.59 (2H, d, J=8 Hz, ArH), 7.33 (1H, dd, J=15 and 10 Hz, CH=CH-C=O), 7.25 (4H, m, ArH), 7.18 (2H, m, Ph-C*H* and Ph-CH=C*H*), 6.14 (1H, d, J=15 Hz, CH-C=O), 3.98 (3H, s, CH_3O); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 162.78 (C=O), 138.83, 137.47, 132.02, 131.69, 129.21, 128.18, 126.33, 122.05, 120.01, 114.74 (ArC=C and C=C), 55.97 (CH_3O). Elemental analysis: $C_{18}H_{17}N_2O_5SK$,1/2H_2O. Calc (%) C: 51.2, H: 4.27, N: 6.63. Found (%) C: 50.84, H: 4.83, N: 6.73.

Preparation Example 9: (2*E*,4*E*,6*E*)-6-methyl-7-(4-nitrophenyl)hepta-2,4,6-trienoic acid ethyl ester

To a suspension of 3-ethoxycarbonylallylidenetriphenylarsonium bromide (1.0 g, 2.0 mmol) in dry THF (10 mL) was added dropwise *n*-butyllithium (2.5 M in hexanes, 1.1 mL, 2.75 mmol) at 0 °C. Stirring was continued at 0 °C for 20 min, then 10 min at 20 °C. To the above solution was added *(E)*-2-methyl-3-(4-*p*-nitrophenyl) propenal (4b) (0.318 g, 1.66 mmol) in portions over 5 min. The mixture was then stirred at 20 °C for 16 h. The mixture was evaporated and the residue purified by flash chromatography on silica gel (1:4 ethyl acetate: 60-80 °C petroleum ether) to give the title compound (0.28 g, 59%) as yellow prisms, mp 143-144 °C. IR (nujol) ν_{max} 1699 (COOEt), 1620 (C=C), 1504 (NO_2) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.06 (2H, d, *J*= 9.0 Hz, ArH), 7.40 (2H, d, *J*=9.0 Hz, ArH), 7.28 (1H, dd, *J*= 11 and 15 Hz, C*H*=CH-CHO), 6.71 (1H, d, *J*=15 Hz, C*H*-CHO), 6.62 (1H, s, Ph-C*H*), 6.45 (1H, dd, *J*= 11 and 15 Hz, =C(CH_3)-CH=C*H*), 5.91 (1H, d, *J*=15 Hz, =C(CH_3)-C*H*), 4.18 (2H, q, *J*=7 Hz, OCH_2), 2.02 (3H, s, =CCH_3), 1.24 (3H, t, *J*=7 Hz, CH_3CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 165 (COO), 144.87, 144.47, 144.21, 139.13, 133.13, 130.26, 128.28, 123.98, 122.52 (ArC=C and C=C), 60.79 (CH_2O), 14.69, 14.45 (CH_3). Elemental analysis: $C_{16}H_{17}NO_4$. Calc. (%) C: 66.89, H: 5.92, N: 4.87. Found (%) C: 66.59, H: 5.82, N: 4.74.

Preparation Example 10: (2*E*,4*E*,6*E*)-7-(4-aminophenyl)-6-methylhepta-2,4,6-trienoic acid ethyl ester

To a stirred solution of iron(II) sulfate heptahydrate (4.64 g, 16.7 mmol) in water (10 mL) and 0.880 concentrated aqueous ammonia (10 mL) at 60 °C was added a solution of (2*E*,4*E*,6*E*)-6-methyl-7-(4-nitrophenyl)hepta-2,4,6-trienoic acid ethyl ester (Preparation Example 9) (0.40 g, 1.39 mmol) in ethanol (10 mL). The mixture was then heated to 60 °C for 15 min. The solution was allowed to cool, extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was recrystallised from methanol to give the title compound (0.32 g, 90%) as orange needles, mp 123-124 °C. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.35 (1H, dd, *J*=11 and 15 Hz, C*H*=CH-COO), 7.15 (2H, d, *J*= 8 Hz, ArH), 6.67 (1H, d, *J*=15 Hz, CH-COO), 6.64 (2H, d, *J*=8 Hz, ArH), 6.60 (1H, s, Ph-CH), 6.31 (1H, dd, *J*=11 and 15 Hz, C*H*-CH=CH-COO), 5.84 (1H, d, *J*=15 Hz, Ph-CH=C(CH_3)-

C*H*), 4.14 (2H, q, *J*=7 Hz, CH_2O), 3.67 (2H, br s, NH_2), 2.00 (3H, s, CH_3), 1.28 (3H, t, *J*=7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.78 (COO), 147.32, 146.33, 145.76, 136.73, 132.86, 131.29, 127.98, 124.75, 119.88, 115.13 (ArC=C and CH=CH), 60.54 (CH_2O), 14.75 and 14.29 (CH_3). Elemental analysis: $C_{16}H_{19}NO_2$, 1/16H_2O. Calc. (%) C: 74.70, H: 7.39, N: 5.44. Found (%) C: 74.38, H: 7.40, N: 5.42.

Example 16: (2*E*,4*E*,6*E*)-7-(4-(4-methoxybenzenesulfonylamino)phenyl)-6-methylhepta-2,4,6-trienoic acid ethyl ester (17h)

A stirred solution of (2*E*,4*E*,6*E*)-7-(4-aminophenyl)-6-methylhepta-2,4,6-trienoic acid ethyl ester (Preparation Example 10) (0.55 g, 2.14 mmol) and *p*-methoxybenzenesulfonyl chloride (0.531 g, 2.57 mmol) in pyridine (5 mL) was heated at reflux for 12 h. The pyridine was removed under reduced pressure and the residue dissolved in dichloromethane (20 mL). The solution was washed with 1.2 M hydrochloric acid (2 x 10 mL) then with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica gel (3:7 ethyl acetate: 60-80 °C petroleum ether) to give the title compound (0.66 g, 72%) as an oil, a mixture of diastereoisomers.

Example 17: (2*E*,4*E*,6*E*)-7-(4-(4-chlorobenzoylamino)phenyl)hepta-2,4,6-trienoic acid methyl ester (17s)

4-Chloro-*N*-(4-formylphenyl)benzamide (Preparation Example 1; 2g) (0.27 g, 1.05 mmol), [(2*E*,4*E*)-6-methoxy-6-oxo-2,4-hexadienyl]triphenylphosphonium bromide (0.49 g, 1.05 mmol) and potassium carbonate (0.72 g, 5.22 mmol) were added to THF (20 mL). The mixture was stirred at 40 °C for 72 h. The solvent was evaporated and the residue was suspended in ethyl acetate (50 mL), sonicated for 10 min, and stirred for 1 h at 20 °C. The mixture was then filtered through a thin pad of silica, which was subsequently washed with ethyl acetate 2 x 10 mL. The combined filtrates were evaporated, and the residue recrystallised from isopropanol to give the title compound (0.12 g, 31 %) as a yellow prisms, mp 169-170 °C.

Preparation Example 11: ethyl 5-(4-aminophenyl)-4-methylpentanoate (25a)

Ethyl 4-methyl-5-(4-nitrophenyl)penta-2,4-dienoate (Preparation Example 3, **6c**) (1.80 g, 6.89 mmol) was dissolved in ethanol (50 mL), and a catalytic amount of 10%

palladium-on-carbon was added cautiously. Nitrogen gas was passed over the mixture. A gentle vacuum was then applied for a short time. Nitrogen gas was then slowly admitted and the gas above the mixture then evacuated. Hydrogen was then carefully admitted until atmospheric pressure reached. The mixture was stirred under hydrogen (1 atm) for 2 h. The hydrogen gas was then evacuated and replaced by nitrogen. The mixture was filtered through Celite® and the solvent evaporated to give the title compound (1.51 g, 97%) as a clear oil. ^{1}H NMR (300 MHz) δ_H 6.93 (d, 2H, 2,6-Ar), 6.60 (d, 2H, 3,5-Ar), 4.08 (q, 2H, CO-OCH_2-CH_3), 3.48(s, broad, 2H, NH_2), 2.52 (q, 1H, Ar-CH_2-CHMe-), 2.30 (m, 3H, Ar-CH_2-CHMe- and -CH_2CO_2Et), 1.69 (m, 2H, -CHMe-CH_2-CH_2-CO_2Et), 1.47 (m, 1H, Ar-CH_2-CHMe-CH_2-), 1.24 (t, 3H, -COO-CH_2-CH_3), 0.84 (d, 3H, -CH_2-CHMe-CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.97 (C1), 144.24 (4-Ar), 130.97 (1-Ar), 129.91 (3,5-Ar), 115.11 (2,6-Ar), 60.20 (O-CH_2-CH_3), 42.50 (C5), 34.78 (C4), 32.28 (C3), 31.59 (C2), 18.99 (C6), 14.25 (O-CH_2-CH_3).

Example 18: 5-[4-(4-methoxybenzenesulfonylamino)phenyl]-4-methylpentanoic acid ethyl ester (25c)

Ethyl 5-(4-aminophenyl)-4-methylpentanoate (Preparation Example 11, 25a) (0.65 g, 2.76 mmol) was dissolved in pyridine (4.0 mL), and 4-methoxybenzenesulfonyl chloride (0.57 g, 2.76 mmol) was added to the stirred mixture. The mixture was stirred for an additional 16 h at 25 °C. The pyridine was removed under a high vacuum and the residue was dissolved in dichloromethane (50 mL). This solution was washed with 2M hydrochloric acid (3 x 20 mL), then with water (20 mL) and lastly with saturated aqueous sodium hydrogen carbonate (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give a residue that was purified by flash chromatography (gradient elution from pure 40-60 °C petroleum ether to 40:60: ethyl acetate: 40-60 °C petroleum ether with 5% increase in ethyl acetate for every 200 mL) to give the title compound (0.78 g, 70%) as a yellow oil.

Example 19: Ethyl 5-[4-(4-chlorobenzoylamino)phenyl]-4-methylpentanoate (25d)

Ethyl 5-(4-aminophenyl)-4-methylpentanoate (Preparation Example 11, 25a) (0.54 g, 2.29 mmol) was dissolved in pyridine (4.0 mL), and 4-chlorobenzoyl chloride (0.52 g, 2.97 mmol) was added to the stirred mixture. The mixture was stirred for an additional 16 h at 25 °C. The pyridine was removed under a high vacuum and the

residue was dissolved in dichloromethane (50 mL). This solution was washed with 2M hydrochloric acid (3 x 20 mL), then with water (20 mL) and lastly with saturated aqueous sodium hydrogen carbonate (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The pink residue was recrystallised from propan-2-ol to give the title compound (0.48 g, 56%) as shiny white platelets, mp 114-115 °C. ^{1}H (300 MHz) δ_H 8.06(s, 1H, CO-NH-Ar), 7.76 (d, 2H, 2,6-Ar), 7.51 (d, 2H, 3,5-Ar), 7.40 (d, 2H, 3,5-Ar), 7.10 (d, 2H, 2,6-Ar), 4.10 (q, 2H, O-CH_2-CH_3), 2.61 (q, 1H, Ar-CH_2-CHMe-), 2.34 (m, 3H, Ar-CH_2-CHMe- and -CH_2CO_2Et), 1.72 (m, 2H, -CHMe-CH_2-CH_2-CO_2Et), 1.46 (m, 1H, Ar-CH_2-CHMe-CH_2-), 1.24 (t, 3H, -COO-CH_2-CH_3), 0.85 (d, 3H, -CH_2-CHMe-CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.93 (C1), 164.76 (CONH), 137.93 (4-Ar), 137.50 (4-Ar), 135.65 (1-Ar), 133.45 (1-Ar), 129.67 (2,6-Ar), 128.91 (2,6-Ar), 128.63 (3,5-Ar), 120.39 (3,5-Ar), 60.29 (O-CH_2-CH_3), 42.79 (C5), 34.61 (C4), 32.21 (C3), 31.58 (C2), 18.97 (C6), 14.25 (O-CH_2-CH_3).

Preparation Example 12: ethyl 5-[4-(4-chlorobenzenesulfonylamino)phenyl]-4-methylpentanoate (25b)

Ethyl 5-(4-aminophenyl)-4-methylpentanoate (Preparation Example 11, 25a) (0.52 g, 2.21 mmol) was dissolved in pyridine (2.0 mL), and a solution of 4-chlorobenzenesulfonyl chloride (0.61 g, 2.89 mmol) in pyridine (2.0 mL) was added to the stirred mixture. The mixture was stirred for an additional 16 h at 25 °C. The pyridine was removed under a high vacuum and the residue was dissolved in dichloromethane (50 mL). This solution was washed with 2 M hydrochloric acid (3 x 20 mL), then with water (20 mL) and lastly with saturated aqueous sodium hydrogen carbonate (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The orange oil was purified by flash chromatography on 70 g of silica gel (gradient elution from pure 60-80 °C petroleum ether to 40:60: ethyl acetate: 60-80 °C petroleum ether). Evaporation of the intermediate fractions afforded the title compound (0.52 g, 57%) as an light yellow oil. ^{1}H (300 MHz) δ_H 7.66 (d, 2H, 2,6-Ar), 7.37 (2, 2H, 3,5-Ar), 6.99 (dd, 4H, 2,6-Ar), 5.29 (s, 1H, SO_2NH), 4.10 (q, 2H, O-CH_2-CH_3), 2.56 (q, 1H, Ar-CH_2-CHMe-), 2.31(m, 3H, Ar-CH_2-CHMe- and -CH_2CO_2Et), 1.66 (m, 2H, -CHMe-CH_2-CH_2-CO_2Et), 1.45 (m, 1H, Ar-CH_2-CHMe-CH_2-), 1.23(t, 3H, -COO-CH_2-CH_3), 0.80 (d, 3H, -CH_2-CHMe-CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.85 (C1), 139.42 (4-Ar), 138.87 (1-Ar), 137.59 (4-Ar), 133.81 (1-Ar), 130.05 (2,6-Ar), 129.24 (2,6-Ar), 128.70

(3,5), 60.33 (O-CH_2-CH_3), 42.69 (C5), 34.47 (C4), 32.13 (C3), 31.51 (C2), 18.93 (C6), 14.24 (O-CH_2-CH_3).

Example 20: 5-[4-(4-chlorobenzenesulfonylamino)phenyl]-4-methylpentanoic acid hydroxyamide (26b)

Ethyl 5-[4-(4-chlorobenzenesulfonylamino)phenyl]-4-methylpentanoate (Preparation Example 12, **25b**) (0.63 g, 1.53 mmol) was dissolved in methanol (5.0 mL) at 0 °C. The solution was stirred and 50% aqueous hydroxylamine (0.91 g, 13.8 mmol) was added dropwise over 15 min, and then aqueous potassium hydroxide (1.3 mL, 1.6 M) in methanol added to the mixture in one batch. The stirred mixture was allowed to warm up to 25° C over 14 h. Water (10 mL) was then added, and dilute hydrochloric acid added until pH 6 was attained. The mixture was extracted with 85:15 ethyl acetate: methanol (5 x 30 mL) and the combined organic layers dried ($MgSO_4$), filtered and evaporated to give the title compound (0.32 g, 52%) as an oil.

Example 21: 5-[4-(4-chlorobenzoylamino)phenyl]-4-methylpentanoic acid hydroxyamide (26d)

Ethyl 5-[4-(4-chlorobenzoylamino)phenyl]-4-methylpentanoate (Example 19; **25d**) (0.52 g, 1.39 mmol) was dissolved in methanol (5.0 mL) at 0 °C. The solution was stirred and 50% aqueous hydroxylamine (0.84 g, 12.7 mmol) was added dropwise over 15 min, and then aqueous potassium hydroxide (1.3 mL, 1.6 M) in methanol added to the mixture in one batch. The stirred mixture was allowed to warm up to 25° C over 14 h. Water (10 mL) was then added, and dilute hydrochloric acid added until pH 6 was attained. The mixture was extracted with 85:15 ethyl acetate: methanol (5 x 30 mL) and the combined organic layers dried ($MgSO_4$), filtered and evaporated. The residue was recrystallised from methanol/hexane, to give the title compound (0.21 g, 41%) as a fine white powder, mp 185-186 °C.

Example 22: *(2E,4E,6E)*-7(4-(*p*-Chlorobenzenesulphonylamino)-6-methylhepta-2,4,6-trienoic acid ethyl ester

A solution of (*2E,4E,6E*)-7(*p*-aminophenyl)-6-methylhepta-2,4,6-trienoic acid ethyl ester (0.37 g, 1.44 mmol) and *p*-chlorobenzenesulphonylchloride (0.365 g, 2.88 mmol) in pyridine (5 mL) was heated at reflux for 24 h. Stirring was then continued for

an additional 48 h at room temperature. After the removal of the pyridine under vacuum, the residue was dissolved in dichloromethane (30 mL), washed with 1.2 M hydrochloric acid, and the organic layer dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel column using 1:4 ethyl acetate:40-60 °C petroleum ether to give the title compound (0.40 g, 64%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.94 (2H, d, J=8 Hz, ArH), 7.59 (3H, m, ArH and C*H*=CH-C=O), 7.41 (2H, d, J=8 Hz, ArH), 7.29 (2H, d, J=8 Hz, ArH), 6.86 (1H, d, J=15 Hz, C(CH_3)-CH=), 6.84 (1H, s, Ph-CH), 6.70 (1H, dd, J=15 and 11 Hz, C(CH_3)-CH=CH), 6.11 (1H, d, J=15 Hz, CH-C=O), 4.39 (2H, t, J=7 Hz, CH_2O), 2.08 (3H, s, CH_3), 1.47 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.86 (C=O), 146.29, 145.40, 140.03, 137.91, 135.80, 135.58, 134.97, 134.84, 130.86, 129.80, 129.08, 126.36, 121.58, 121.00 (ArC=C and C=C), 60.83 (CH_2O), 14.72, 14.26 (CH_3).

__Determination of Histone Deacetylase Inhibition Activity__

Histone deacetylase inhibitory activity was measured as described by Vigushin *et al.*, *Clin. Cancer Res.*, 7, 971-976 (2001) based on methods published by Taunton *et al.*, Science, 272, 408-411 (1995) and Emiliani *et al*, *Proc. Natl. Acad. Sci. U.S.A.*, 95, 2795-2800 (1998). Briefly, the assay begins by incubating histone deacetylase enzymes contained in a nuclear extract from the HeLa human cervical adenocarcinoma cell line with a compound of the invention followed by addition of a radiolabeled substrate. The substrate was a synthetic peptide corresponding to histone H4 (amino acids 14-21) that had been chemically acetylated on lysine residues with sodium [^{3}H]acetate according to the method published by Taunton *et al.*, *Science* 272, 408-411 (1995). Released [^{3}H] acetic acid (a measure of histone deacetylase activity) was then extracted with ethyl acetate and quantified in a scintillation counter. The concentration of a compound of the invention that inhibits histone deacetylase activity by 50% (i.e. IC_{50}) was then determined by repeating the assay with a range of different concentrations of compound. Each assay was performed in duplicate with control samples in triplicate for accuracy.

__HeLa cell nuclear extract__

HeLa cell nuclear extract was prepared according to the method of Dignam *et al*, *Nucleic Acids Res.*, 11, 1475-1489 (1983). HeLa human cervical adenocarcinoma cells

were grown at 37°C in DMEM medium containing 5% foetal calf serum to a concentration of $5x10^5$ cells per ml prior to harvesting. Cells were then harvested by centrifugation for 10 minutes at 2,000 rpm in a Sorvall HG4L rotor. The cell pellet was resuspended in 5 volumes of cold phosphate buffered saline, collected by centrifugation at 4°C and all subsequent manipulations were performed at 4°C. Cells were suspended in 5 packed cell volumes of 10mM HEPES (pH 7.9 at 4°C), 1.5 mM $MgCl_2$, 10mM KCl and 0.5 mM DDT and allowed to equilibrate for 10 minutes. The cells were pelleted by centrifugation as above, resuspended in 2 packed cell volumes of the same buffer and then lysed by 10 strokes of a glass Dounce homogenizer. The homogenate was centrifuged as before and the pellet was then centrifuged for 20 minutes at 25,000 x g in a Sorvall SS34 rotor to remove residual cytoplasmic material, yielding crude nuclei. Crude nuclei from 10^9 cells were resuspended in 3 ml of 20 mM HEPES (pH 7.9), 25% (v/v) glycerol, 420 mM NaCl, 1.5 mM $MgCl_2$, 0.2 mM EDTA, 0.5 mM phenylmethylsulfonyl fluoride (PMSF) and 0.5 mM DTT with a glass Dounce homogenizer (10 strokes). After stirring gently with a magnetic stirrer for 30 minutes, the suspension was centrifuged for 30 minutes at 25,000 x g (Sorvall SS34 rotor). The supernatant was dialysed against 50 volumes at 20 mM HEPES (pH 7.9), 20% (v/v) glycerol, 100 mM KCl, 0.2 mM EDTA, 0.5 mM PMSF and 0.5 mM DTT for 5 hours and the dialysate was then centrifuged at 25,000 x g for 20 minutes (Sorvall SS34 rotor). The supernatant, designated the nuclear extract, was snap frozen in liquid nitrogen and then stored at –80°C. The protein concentration measured by Bradford assay was 10 mg/ml and 50 mg of protein was obtained from 10^9 cells.

Acetylation of histone H4 peptide with [^{3}H]acetate

A peptide corresponding to amino-terminal residues 14-21 of histone H4 (GAKRHRKV) was synthesised in an automated peptide synthesiser (ABI 433; Applied Biosystems, Cheshire, UK), purified by reverse phase high performance liquid chromatography (HPLC), and lyophilised. The peptide was >95% pure by reverse phase HPLC, mass spectrometry and capillary electrophoresis. All subsequent steps were performed in a fume hood. To 1 mg of the lyophilised peptide in a 2 ml screw top amber glass vial was added 500 µl (12.5 mCi) of sodium [^{3}H]acetate (9.9 Ci/mmol, 25 mCi/ml in ethanol; ICN Pharmaceuticals, Basingstoke, UK). Then 20 µl of a freshly prepared solution of 0.24 M benzotriazol-1-yloxytris(dimethylamino)phosphonium

hexafluorophosphate (BOP reagent; Sigma-Aldrich, Gillingham, UK) and 0.2 M triethylamine in acetonitrile was added, the reaction vial was capped, and the labelling mixture incubated on a rotating platform overnight at room temperature. The mixture was then concentrated to dryness under reduced pressure and the residue dissolved in 1 ml TEN buffer (50 mM Tris (pH 8.0), 150 mM NaCl, 5 mM EDTA). After centrifugation at 14,000 x g for 15 seconds at room temperature, the supernatant containing [^{3}H]acetate-labelled histone H4 peptide was purified by gel filtration on Sephadex G-25 (PD10 column; Amersham Biosciences UK Limited, Buckinghamshire, UK). After equilibrating with 10 column volumes of TEN, the supernatant was loaded onto the column and then eluted with TEN. 0.5 ml fractions were collected and the radioactivity in each was quantified by liquid scintillation counting. After the column void volume, the [^{3}H]acetate-labelled histone H4 peptide elutes first followed by free unincorporated label ([^{3}H]acetic acid). Eluates containing the purified radiolabeled peptide are pooled, divided into aliquots and stored at –70°C until use.

Histone deacetylase assay

Histone deacetylase inhibition by compounds of the invention was assayed as described in Vigushin *et al., Clin Cancer Res.* 7, 971-976 (2001) based on methods published by Taunton *et al., Science,* 272, 408-411 (1995) and Emiliani *et al.. Proc. Natl. Acad. Sci. U.S.A.*, 95, 2795-2800 (1998). HeLa cell nuclear extract prepared according to Dignam *et al*, Nucleic Acids. Res. 11, 1475-1489 (1983) was used as a source of histone deacetylase enzymes. The substrate was a synthetic peptide corresponding to amino acids 14-21 of histone H4 that had been chemically acetylated on lysine residues with sodium [^{3}H]acetate as described by Taunton *et al., Science* 272, 408-411 (1995). A stock solution in dimethylsulfoxide (DMSO) was prepared for each compound of the invention to be tested and trichostatin A as a positive control. Stock solutions were diluted in DMSO to give a range of 100x working solutions.

The assay was performed in a final reaction volume of 200 µl. To each tube was added 40 µl of 5x HDAC buffer (50 mM Tris (pH 8.0), 750 mM NaCl, 50% (v/v) glycerol, 1 mM PMSF], 4 µl (40 µg total protein) HeLa cell nuclear extract, 2 µl 100x inhibitor in DMSO or 2 µl DMSO as a negative control, and water to a total of 199 µl. After mixing by vortex and brief centrifugation (14,000 x g for 5 seconds at room temperature), the reaction mixture was incubated for 30 minutes at room temperature.

The assay was then initiated by addition of 1 µl (37 kBq) of [^{3}H]acetate-labelled histone H4 peptide substrate. After brief vortex and centrifugation as above, the reaction mixture was incubated for 60 minutes at room temperature. Fifty µl of a quenching solution [1 M HCl/0.16 M acetic acid] was then added to stop the reaction. The released [^{3}H]acetate in each assay reaction was extracted into 600 µl ethyl acetate. After mixing by vortex, the organic and aqueous phases were separated by centrifugation (14,000 x g for 1 minute at room temperature). Duplicate 200 µl aliquots of the upper organic phase were transferred into separate scintillation vials each containing 5 ml scintillant (Hionic Fluor; Canberra Harwell Ltd., Didcot, UK) and the radioactivity in each measured by β-scintillation counting.

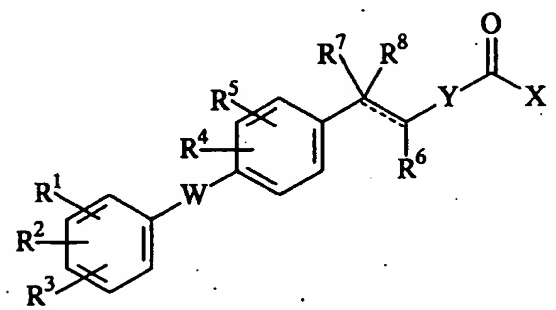
An initial assay was performed to established the range of activity of each compound of the invention. The assay was then repeated using four log dilutions in range according to the expected potency for each test compound. The concentration of each compound of the invention that inhibited histone deacetylase enzyme activity by 50% (IC_{50}) was determined graphically in each case using non-linear regression analysis to fit inhibition data to the appropriate dose-response curve (GraphPad Prism Version 3.0; GraphPad Software Inc., San Diego, CA). Each test compound was assayed in duplicate whilst positive and negative control samples were assayed in triplicate.

Test compounds of the invention were found to be potent histone deacetylase inhibitors, some having IC_{50} values in the low nanomolar concentration range (e.g. two test compounds had IC_{50} values of 49 nM and 74 nM).

Compound	IC_{50}	± SE
Example 5	>100 µM	
Example 12	172 nM	35
Example 13	49 nM	4
Example 14	74 nM	16
Example 15	10.4 µM	1.3

CLAIMS

1. Use of a compound of formula (I) for the manufacture of a medicament for use in treating a disorder mediated by histone deacetylase:



(I)

wherein:

- the symbol ---- represents a single bond or a double bond or the symbol ----, R^6 and R^8 together represent cyclopropyl;

- R^1 to R^5 each independently represent hydrogen, C_2-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, C_1-C_{10} hydroxyalkyl, halo, C_1-C_{10} haloalkyl, amino, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amido, nitro, cyano, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, (C_1-C_{10} alkyl)sulfinyl, (C_1-C_{10} alkyl)sulfonyl or C_1-C_{10} alkyl substituted by amino, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino or di(C_1-C_{10} alkyl)amino, and wherein one or two of R^1, R^2 and R^3 is/are hydrogen and the other one or two of R^1, R^2 and R^3 is/are other than hydrogen;

- R^6 represents hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, an unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double or triple bond, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, halo, cyano, nitro, amino, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amido, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, (C_1-C_{10} alkyl)sulfinyl, (C_1-C_{10} alkyl)sulfonyl, a saturated or unsaturated C_3-C_{12} hydrocarbon chain interrupted by O, S, NR, CO, C=NR, N(R)SO_2, SO_2N(R), N(R)C(O)O, OC(O)N(R), N(R)C(O)N(R), OC(O), C(O)O, OSO_2, SO_2O or OC(O)O where:

(a) R independently represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, hydroxyl or C_1-C_{10} haloalkyl, and

(b) the saturated or unsaturated hydrocarbon chain is optionally substituted with C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, hydroxyl, C_1-C_{10} hydroxyalkyl, halo, C_1-C_{10} haloalkyl, amino, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl or C_1-C_{10} alkylsulfonyl,

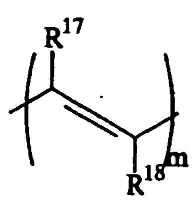
- when the symbol ---- represents a single bond, R^7 and R^8 each independently represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} each independently represent hydrogen or C_1-C_6 alkyl or one of R^9 and R^{10} is H and the other is $-CO(C_1$-C_6 alkyl). or R^7 and R^8 together represent =O, $=CH_2$ or $=CHR^9$ wherein R^9 is as defined above;

- when the symbol ---- represents a double bond, R^7 represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} are as defined above and R^8 is absent;

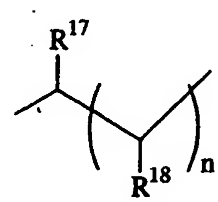
- W represents a single bond, $-C(R^{11})=N-$, $-N=C(R^{11})-$, $-C(R^{11})(R^{12})-NR^{13}-$, $-NR^{13}-C(R^{11})(R^{12})-$, $-CO-NR^{11}-$, $-NR^{11}-CO-$, $-SO_2-NR^{11}-$, $-NR^{11}-SO_2-$, $-C(R^{11})(R^{12})-O-$, $-O-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-S-$, $-S-C(R^{11})(R^{12})-$, $-CO-$, $-NR^{11}-$, $-SO-$, $-SO_2-$, S or $-[C(R^{11})R^{12}]_p-$ wherein R^{11}, R^{12} and R^{13} each independently represents hydrogen, C_1-C_6 alkyl, C_6 or C_{10} aryl or a 5- to 10- membered heterocyclic group alkyl and p is an integer of from 1 to 4;

- X represents $-OR^{14}$, $-SR^{14}$, $-NR^{14}OR^{15}$, $-NR^{14}NR^{15}R^{16}$, $-CF_3$, $-CF_2H$ or CH_2F wherein R^{14}, R^{15} and R^{16} each independently represents hydrogen or C_1-C_6 alkyl; and

- Y represents



or



wherein m is an integer from 1 to 4; n is an integer from 1 to 8; and R^{17} and R^{18} each independently represents hydrogen, unsubstituted or substituted C_1-C_{10} alkyl, an

unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double and/or triple bonds, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, halo, cyano, nitro, amino, amido, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, C_1-C_{10} alkylsulfinyl, C_1-C_{10} alkylsulfonyl, or a saturated or unsaturated C_3-C_{12} hydrocarbon chain interrupted by O, S, NR, CO, C(NR), N(R)SO_2, SO_2N(R), N(R)C(O)O, OC(O)N(R), N(R)C(O)N(R), OC(O), C(O)O, OSO_2, SO_2O or OC(O)O where R is as defined above and the saturated or unsaturated hydrocarbon chain is optionally substituted as defined above;
and pharmaceutically acceptable salts thereof.

2. Use according to claim 1, wherein R^1, R^2 and R^3 are selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, halo, C_1-C_6 haloalkyl, (C_1-C_6 alkoxy)carbonyl or C_1-C_6 alkyl substituted by amino, C_1-C_6 alkoxy, C_1-C_6 alkylamino or di(C_1-C_6 alkyl) amino.

3. Use according to claim 1 or claim 2, wherein R^4 and R^5 are selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, C_1-C_6 haloalkyl or C_1-C_6 alkyl substituted by amino, C_1-C_6 alkoxy, C_1-C_6 alkylamino or di(C_1-C_6 alkyl) amino.

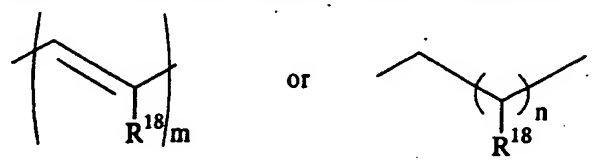
4. Use according to any one of the preceding claims, wherein either or both of R^4 and R^5 is hydrogen.

5. Use according to any one of the preceding claims, wherein R^{11}, R^{12} and R^{13} are each independently selected from hydrogen, methyl or ethyl.

6. Use according to any one of the preceding claims, wherein W represents -CH=N-, -CONH-, -SO_2NH-, -CH_2O- or –CH_2S-.

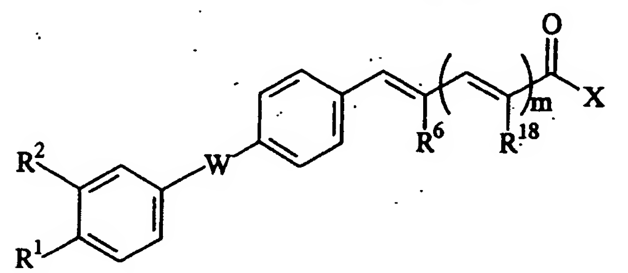
7. Use according to any one of the preceding claims, wherein X represents -CF_3, -OR^5 or -NHOR^5 wherein R^5 is hydrogen or C_1-C_6 alkyl.

8. Use according to any one of the preceding claims, wherein Y represents:



wherein m is 1, 2 or 3; n is 1, 2 or 3; and R^{18} is hydrogen, C_1-C_6 alkyl or C_1-C_6 alkoxy.

9. Use according to claim 1, wherein the compound is of formula (II):

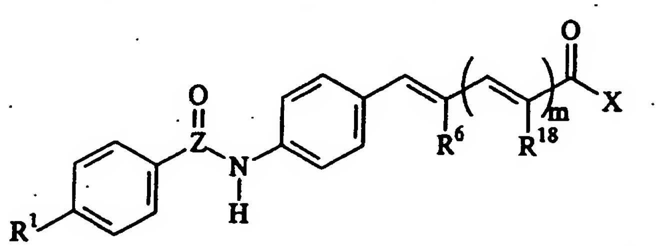


(II)

wherein R^1, R^2, R^6, R^{18}, W and X are as defined above and m is 1, 2 or 3; and pharmaceutically acceptable salts thereof.

10. Use according to claim 9, wherein R^1 and R^2 independently represent hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo or (C_1-C_6 alkoxy)carbonyl; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; W represents a single bond, -CH=N-, N=CH-, -CONH-, -NHCO-, $-SO_2NH-$, $-NHSO_2-$, $-OCH_2-$, $-CH_2O-$, $-CH_2S-$ or $-SCH_2-$; and X represents–NHOH, $-CF_3$ or $-OR^{14}$ wherein R^{14} is hydrogen or C_1-C_4 alkyl.

11. Use according to claim 9, wherein the compound is of formula (III):



(III)

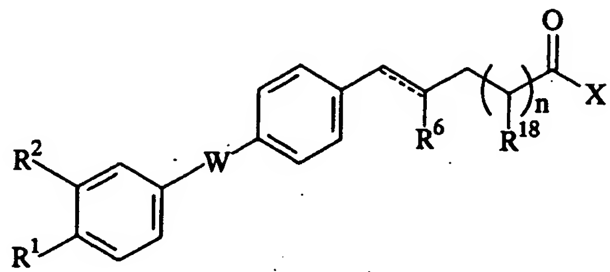
wherein R^1 represents C_1-C_4 alkyl, C_1-C_4 alkoxy or halo; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; X represents $-OR^{14}$

or –NHOH wherein R^{14} is hydrogen or C_1-C_4 alkyl; Z represents C or SO; and m is 1, 2 or 3; and pharmaceutically acceptable salts thereof.

12. Use according to claim 11, wherein R^6 is methyl.

13. Use according to claim 11, wherein the compound is selected from:
(2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)penta-2,4-dienoic acid ethyl ester;
(2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)penta-2,4-dienoic acid ethyl ester;
(2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester;
(2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid;
(2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester;
(2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-2,4-dimethylpenta-2,4-dienoic acid ethyl ester;
(2*E*,4*E*)-5-(4-(4-methoxybenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid;
(2*E*,4*E*)-5-(4-(4-chlorobenzenesulfonylamino)phenyl)-4-methylpenta-2,4-dienoic acid ethyl ester;
(2*E*,4*E*)-5-(4-methoxybenzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid hydroxamide;
(2*E*,4*E*,6*E*)-7-(4-(4-methoxybenzenesulfonylamino)phenyl)-6-methylhepta-2,4,6-trienoic acid ethyl ester; and
(2E,4E,6E)-7-(4-(4-chlorobenzoylamino)phenyl)hepta-2,4,6-trienoic acid methyl ester.

14. Use according to claim 1, wherein the compound is of formula (IV):

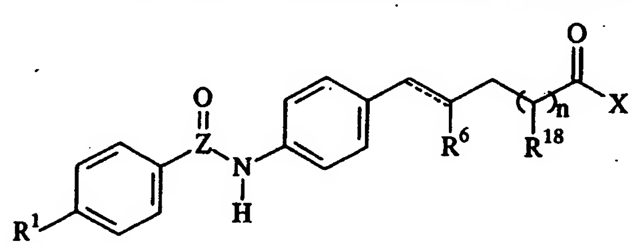


(IV)

wherein R^1, R^2, R^6, R^{18}, W and X as defined in claim 1, the symbol ---- represents a single bond or a double bond and n is 1, 2 or 3; and pharmaceutically acceptable salts thereof.

15. Use according to claim 14, wherein R^1 and R^2 each independently represent hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo or (C_1-C_6 alkoxy)carbonyl; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; W represents a single bond, -CH=N-, -N=CH-, CONH-, -NHCO-, $-SO_2NH-$, $-NHSO_2-$, $-OCH_2-$, $-CH_2O-$, $-CH_2S-$ or $-SCH_2-$; and X represents –NHOH, CF_3 or $-OR^{14}$ wherein R^{14} is hydrogen or C_1-C_4 alkyl.

16. Use according to claim 14, wherein the compound is of formula (V):



(V)

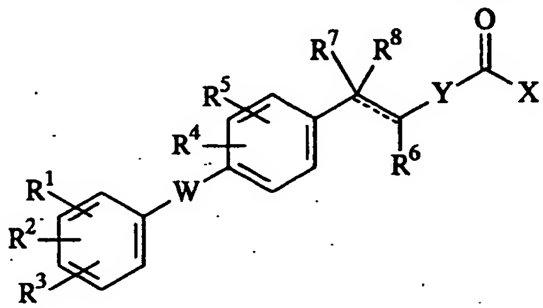
wherein the symbol ---- represents a single bond or a double bond; R^1 represents C_1-C_4 alkyl, C_1-C_4 alkoxy or halo; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; X represents $-OR^{14}$ or -NHOH wherein R^{14} is hydrogen or C_1-C_4 alkyl; Z represents C or SO; and n is 1, 2 or 3; and pharmaceutically acceptable salts thereof.

17. Use according to claim 16, wherein R^6 is methyl.

18. Use according to claim 16, wherein the compound is selected from:

5-[4-(4-methoxybenzenesulfonylamino)phenyl]-4-methylpentanoic acid ethyl ester;
ethyl 5-[4-(4-chlorobenzenesulfonylamino)phenyl]-4-methylpentanoate;
ethyl 5-[4-(4-chlorobenzoylamino)phenyl]-4-methylpentanoate;
5-[4-(4-chlorobenzenesulfonylamino)phenyl]-4-methylpentanoic acid hydroxyamide; and
5-[4-(4-chlorobenzoylamino)phenyl]-4-methylpentanoic acid hydroxyamide.

19. Use of a compound of formula (VI) for the manufacture of a medicament for use in treating a disorder mediated by histone deacetylase:



(VI)

wherein

- the symbol ---- represents a single bond or a double bond or the symbol ----, R^6 and R^8 together represent cyclopropyl;
- R^1 to R^5 each independently represent hydrogen, C_2-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, C_1-C_{10} hydroxyalkyl, halo, C_1-C_{10} haloalkyl, amino, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amido, nitro, cyano, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, (C_1-C_{10} alkyl)sulfinyl, (C_1-C_{10} alkyl)sulfonyl or C_1-C_{10} alkyl substituted by amino, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino or di(C_1-C_{10} alkyl)amino;
- R^6 represents hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, an unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double or triple bond, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, halo, cyano, nitro, amino, C_1-C_{10} alkylamino, di(C_1-C_{10} alkyl)amino, amido, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, (C_1-C_{10} alkyl)sulfinyl, (C_1-C_{10} alkyl)sulfonyl, a saturated or unsaturated C_3-C_{12} hydrocarbon chain interrupted by O, S, NR, CO, C=NR, $N(R)SO_2$, $SO_2N(R)$,

N(R)C(O)O, OC(O)N(R), N(R)C(O)N(R), OC(O), C(O)O, OSO_2, SO_2O or OC(O)O where:

(a) R independently represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, hydroxyl or C_1-C_{10} haloalkyl, and

(b) the saturated or unsaturated hydrocarbon chain is optionally substituted with C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, hydroxyl, C_1-C_{10} hydroxyalkyl, halo, C_1-C_{10} haloalkyl, amino, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl or C_1-C_{10} alkylsulfonyl,

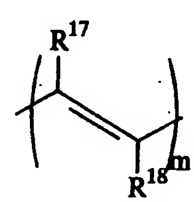
- when the symbol ---- represents a single bond, R^7 and R^8 each independently represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} each independently represent hydrogen or C_1-C_6 alkyl or one of R^9 and R^{10} is H and the other is $-CO(C_1$-C_6 alkyl). or R^7 and R^8 together represent =O, $=CH_2$ or $=CHR^9$ wherein R^9 is as defined above;

- when the symbol ---- represents a double bond, R^7 represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} are as defined above and R^8 is absent;

- W represents a single bond, $-C(R^{11})=N-$, $-N=C(R^{11})-$, $-C(R^{11})(R^{12})-NR^{13}-$, $-NR^{13}-C(R^{11})(R^{12})-$, $-CO-NR^{11}-$, $-NR^{11}-CO-$, $-SO_2-NR^{11}-$, $-NR^{11}-SO_2-$, $-C(R^{11})(R^{12})-O-$, $-O-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-S-$, $-S-C(R^{11})(R^{12})-$, -CO-, $-NR^{11}-$, -SO-, $-SO_2-$, S or $-[C(R^{11})R^{12}]_p-$ wherein R^{11}, R^{12} and R^{13} each independently represents hydrogen, C_1-C_6 alkyl, C_6 or C_{10} aryl or a 5- to 10- membered heterocyclic group alkyl and p is an integer of from 1 to 4;

- X represents $-OR^{14}$, $-SR^{14}$, $-NR^{14}OR^{15}$, $-NR^{14}NR^{15}R^{16}$, $-CF_3$, $-CF_2H$ or CH_2F wherein R^{14}, R^{15} and R^{16} each independently represents hydrogen or C_1-C_6 alkyl; and

- Y represents



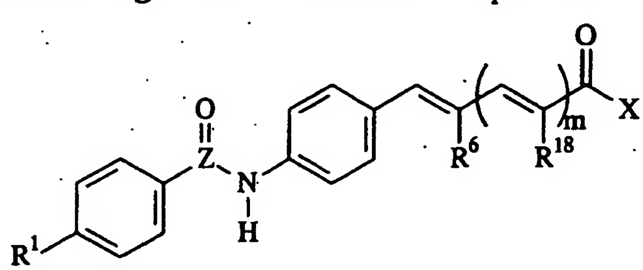
wherein m is an integer from 1 to 4; n is an integer from 1 to 8; and R^{17} and R^{18} each independently represents hydrogen, unsubstituted or substituted C_1-C_{10} alkyl, an unsaturated hydrocarbon chain of up to ten carbon atoms comprising one or more carbon-carbon double and/or triple bonds, C_6 or C_{10} aryl, a 5- to 10-membered heterocyclic group, C_1-C_{10} alkoxy, C_1-C_{10} thioalkoxy, hydroxyl, halo, cyano, nitro, amino, amido, (C_1-C_{10} alkyl)carbonyloxy, (C_1-C_{10} alkoxy)carbonyl, (C_1-C_{10} alkyl)carbonyl, (C_1-C_{10} alkyl)thiocarbonyl, (C_1-C_{10} alkyl)sulfonylamino, aminosulfonyl, C_1-C_{10} alkylsulfinyl, C_1-C_{10} alkylsulfonyl, or a saturated or unsaturated C_3-C_{12} hydrocarbon chain interrupted by O, S, NR, CO, C(NR), $N(R)SO_2$, $SO_2N(R)$, N(R)C(O)O, OC(O)N(R), N(R)C(O)N(R), OC(O), C(O)O, OSO_2, SO_2O or OC(O)O where R is as defined above and the saturated or unsaturated hydrocarbon chain is optionally substituted as defined above;
and pharmaceutically acceptable salts thereof.

20. Use according to claim 19 wherein R^1, R^2 and R^3 are selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, halo, C_1-C_6 haloalkyl, (C_1-C_6 alkoxy)carbonyl or C_1-C_6 alkyl substituted by amino, C_1-C_6 alkoxy, C_1-C_6 alkylamino or di(C_1-C_6 alkyl) amino.

21. Use according to claim 19 or claim 20 wherein one or two of R^1, R^2 and R^3 is hydrogen.

22. Use according to any one of claims 19 to 21 and wherein the compound is additionally as defined in any one of claims 3 to 7, 9 or 10.

23. Use according to claim 19 wherein the compound is of formula (VII):



(VII)

wherein R^1 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halo; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; X represents $-OR^{14}$

or –NHOH wherein R^{14} is hydrogen or C_1-C_4 alkyl; Z represents C or SO; and m is 1, 2 or 3; and pharmaceutically acceptable salts thereof.

24. Use according to claim 23 wherein R^6 is methyl

25. Use according to claim 23 wherein the compound is selected from:
(2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid ethyl ester;
(2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid; and
(2*E*,4*E*)-5-(4-benzenesulfonylaminophenyl)-4-methylpenta-2,4-dienoic acid hydroxamide.

26. Use according to any one of the preceding claims, wherein the disorder is a cancer, cardiac hypertrophy, a hematological disorder or a genetic-related metabolic disorder.

27. Use according to claim 26, wherein the cancer is leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, cervical cancer, renal cancer, prostate cancer and breast cancer.

28. A pharmaceutical composition comprising a pharmaceutically acceptable carried or diluent and, as active ingredient, a compound as defined in any one of claims 1 to 25 and which further comprises another chemotherapeutic or antineoplastic agent.

29. A composition according to claim 28, which further comprises a DNA methylation inhibitor.

30. Products containing a compound as defined in any one of claims 1 to 25 and another chemotherapeutic or antineoplastic agent as a combined preparation for simultaneous, separate or sequential use in treating a cancer.

31. Products according to claim 30, wherein the said agent is a DNA methylation inhibitor.

32. A method of treating a histone deacetylase-mediated disorder, which method comprises the step of administering to a subject having a said disorder a therapeutically effective amount of a compound as defined in any one of claims 1 to 25.

33. A method according to claim 32, comprising the further step of administering another chemotherapeutic or antineoplastic agent to said subject suffering from a cancer.

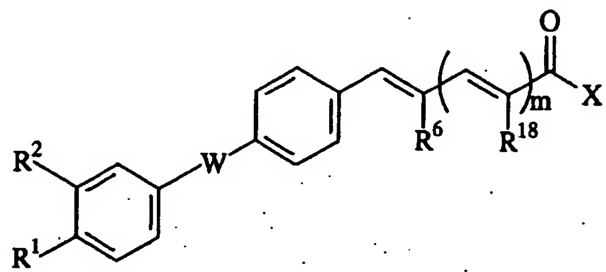
34. A method according to claim 33, wherein the said agent is a DNA methylation inhibitor.

35. A compound of formula (I) as defined in claim 1 wherein:

- when the symbol ---- represents a double bond, R^7 represents hydrogen, halo, C_1-C_{10} alkyl, C_6 or C_{10} aryl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, imidazolyl, pyrazolidinyl, oxadiazolyl, oxazyl, isoxazyl, thiadiazolyl, thiazolyl, 1,2,3-triazolyl, tetrazolyl, pyrazolyl, OR^9, SR^9 or NR^9R^{10} wherein R^9 and R^{10} are as defined above and R^8 is absent; and
- W represents $-C(R^{11})=N-$, $-N=C(R^{11})-$, $-C(R^{11})(R^{12})-NR^{13}-$, $-NR^{13}-C(R^{11})(R^{12})-$, $-CO-NR^{11}-$, $-NR^{11}-CO-$, $-SO_2-NR^{11}-$, $-NR^{11}-SO_2-$, $-C(R^{11})(R^{12})-O-$, $-O-C(R^{11})(R^{12})-$, $-C(R^{11})(R^{12})-S-$, $-S-C(R^{11})(R^{12})-$, $-CO-$, $-NR^{11}-$, $-SO-$, $-SO_2-$, O, S or $-[C(R^{11})R^{12}]_p-$ wherein R^{11}, R^{12} and R^{13} each independently represents hydrogen, C_1-C_6 alkyl, C_6 or C_{10} aryl or a 5- to 10- membered heterocyclic group alkyl and p is an integer of from 1 to 4; and pharmaceutically acceptable salts thereof, with the proviso that that compound is not 6-(4-(4-chlorobenzenesulfonyl amino)phenyl)hex-5-enoic acid or 7-(4-(4-chlorobenzenesulfonylamino)phenyl)hept-6-enoic acid.

36. A compound according to claim 35 and additionally as defined in any one of claims 2 to 9.

37. A compound according to claim 35, having the formula (II):

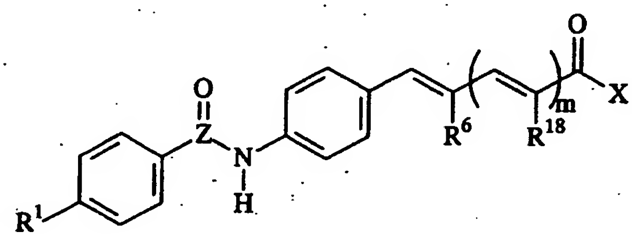


(II)

wherein R^1, R^2, R^6, R^{18}, W and X are as defined above and m is 1, 2 or 3; and pharmaceutically acceptable salts thereof.

38. A compound according to claim 37 wherein R^1 and R^2 independently represent hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo or (C_1-C_6 alkoxy)carbonyl; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; W represents -CH=N-, N=CH-, -CONH-, -NHCO-, $-SO_2NH-$, $-NHSO_2-$, $-OCH_2-$, $-CH_2O-$, $-CH_2S-$ or $-SCH_2-$; and X represents–NHOH, $-CF_3$ or $-OR^{14}$ wherein R^{14} is hydrogen or C_1-C_4 alkyl.

39. A compound according to claim 37, wherein the compound is of formula (III):

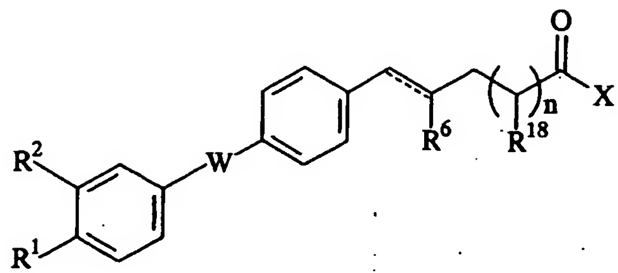


(III)

wherein R^1 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halo; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; X represents $-OR^{14}$ or –NHOH wherein R^{14} is hydrogen or C_1-C_4 alkyl; Z represents C or SO; and m is 1, 2 or 3; and pharmaceutically acceptable salts thereof

40. A compound according to claim 39 and additionally as defined in claim 12 or claim 13.

41. A compound according to claim 35, having the formula (IV):



(IV)

wherein R^1, R^2, R^6, R^{18}, W and X are as defined above, the symbol ----- represents a single bond or a double bond and n is 1, 2 or 3; and pharmaceutically acceptable salts thereof.

42. A compound according to claim 41 wherein R^1 and R^2 each independently represent hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo or (C_1-C_6 alkoxy)carbonyl; R^6 and R^{18} are each independently selected from hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy; W represents -CH=N-, -N=CH-, CONH-, -NHCO-, $-SO_2NH-$, $-NHSO_2-$, $-OCH_2-$, $-CH_2O-$, $-CH_2S-$ or $-SCH_2-$; and X represents –NHOH, CF_3 or $-OR^{14}$ wherein R^{14} is hydrogen or C_1-C_4 alkyl.

43. A compound according to claim 41 and additionally as defined in any one of claims 16 to 18.

44. A compound of formula (VI) as defined in claim 19.

45. A compound according to claim 44 wherein m is 1, 2 or 3 and R^{18} is hydrogen.

46. A compound according to claim 44 or claim 45 and additionally as defined in any one of claims 20 to 25.

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003155

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/10 A61K31/18 A61K31/192 A61K31/195 A61K31/216

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PRABHAKAR, Y. ET AL.: "QSAR study of the role of hydrophobicity in the activity of HMGR inhibitors" XP002301563 Database accession no. 1989:417158 RN: 121308-11-0, 121308-12-1 abstract	28-31, 35,36

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2004	08/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beyss, E

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAKEUCHI, K. ET AL.: "Development of dual-acting agents for thromboxane receptor antagonism and thromboxane synthase inhibition I. Synthesis, structure-activity relationship, and evaluation of substituted omega-phenyl-(3-pyridyl)alkenoic acids" XP002301564 Database accession no. 1995:270973 RN:161607-69-8 abstract	28-31,44
X	DATABASE CAPLUS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002301565 Database accession no. 1994:298479 RN: 140182-56-5, 155066-19-6 abstract & US 5 286 736 A (SOYKA RAINER ET AL) 15 February 1994 (1994-02-15)	28-31,44
X	DATABASE CAPLUS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002301566 retrieved from STN Database accession no. 1992:214360 RN: 140182-56-5 abstract & EP 0 471 259 A (BAYER AG) 19 February 1992 (1992-02-19)	28-31,44

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003155

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 32-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB2004/003155

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